Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c20831949-05**
EudraCT No.	2018-002740-82	
BI Trial No.	1346-0038	
BI Investigational Medicinal Product(s)	BI 425809	
Title	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of BI 425809 once daily with adjunctive Computerized Cognitive Training over 12 week treatment period in patients with schizophrenia	
Lay Title	This study tests whether BI 425809 together with brain training using a computer improves mental functioning in patients with schizophrenia	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted]	
Status	Final Protocol (Revised Protocol (based on Global Amendment 3.0))	
Version and Date:	**Version: 4.0**	**Date: 21 Jul 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	21 Dec 2018
Revision date	21 Jul 2020
BI trial number	1346-0038
Title of trial	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of BI 425809 once daily with adjunctive Computerized Cognitive Training over 12 week treatment period in patients with schizophrenia
Coordinating Investigator:	[redacted]
Trial site(s):	Multi-centre trial
Clinical phase:	II
Trial rationale	This proof of concept (PoC) study will assess whether a drug aimed at improving cognition is better than placebo in patients with schizophrenia on a background of cognitive enrichment with adjunctive Computerized Cognitive Training (CCT).
Trial objective(s)	The primary objective of this trial is to provide PoC data to assess the effect on cognition of oral once daily administration of BI 425809 given for 12 weeks in patients with schizophrenia on stable antipsychotic treatment and adjunctive Computerized Cognitive Training (CCT). Other objectives of this trial are to explore endpoints to assess functioning and well-being of patients with schizophrenia, and to evaluate safety and pharmacokinetics of BI 425809.
Trial endpoints	The primary efficacy endpoint is change from baseline in neurocognitive function as measured by the neurocognitive composite score of the MCCB after 12 weeks of treatment. The secondary endpoints of efficacy and safety are as follows: • Change from baseline in cognitive function as measured by the overall MCCB composite score (including social

	cognition) after 12 weeks of treatment • Change from baseline in the effect of cognitive deficit on day-to-day functioning as measured by SCoRS total score after 12 weeks of treatment • Change from baseline in PANSS total score after 12 weeks of treatment • Percentage of patients with (S)AEs (including clinically relevant abnormalities of physical examination, vital signs, ECG test and laboratory tests)
Trial design	This is a 12-week, multi-center, multi-national, randomized, double-blind, placebo controlled parallel group trial in patients with schizophrenia on stable antipsychotic treatment
Number of patients randomized	200 patients
Number of patients on each treatment	100 patients in active drug treatment arm; 100 patients in placebo drug arm
Diagnosis	Patients with established Schizophrenia (as per Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)) who are clinically stable
Main in- and exclusion criteria	Main inclusion criteria are as follows: 1. Male or female patients who are 18-50 years (inclusive) of age at time of consent 2. Established schizophrenia DSM-5 with the following clinical features: o Outpatient, with no hospitalization for worsening of schizophrenia within 3 months prior to randomization o Psychiatrically stable without symptom exacerbation within 3 months prior to randomization o PANSS score ≤ 5 on positive items P1, P3-P7 and ≤ 4 on positive item P2 at Visit 1, and confirmed at Visit 2 3. Patients must be on stable antipsychotic treatment; also, current antipsychotic medications and concomitant anticholinergics, antiepileptics, lithium and allowed antidepressants must meet the criteria below: o Patients must take 1 and may take up to 2 antipsychotics (typical and/or atypical), except for clozapine (see Section 3.3.3) o Patients must be stable on current antipsychotics, anticholinergics, antiepileptics, lithium and allowed antidepressants for at least 3 months prior to randomization and be on current dose for at least 30 days

	prior to randomization ▪ Patients on long-acting injectable (LAI) antipsychotics should be on the same medication and dose for at least 3 months prior to randomization 4. Patients must demonstrate their ability to properly use the CCT device and program, as well as be compliant with CCT run-in 5. Patients must have a study partner who will preferably be consistent throughout the study Main exclusion criteria are as follows: 1. Patients who have a categorical diagnosis of another current major psychiatric disorder on the M.I.N.I. 2. Patients with a history of participating in any formal cognitive remediation program for 10 or more training sessions 3. Patients who were treated with any of the following medications within the last 6 months prior to randomization: o Bitopertin, BI 409306, encenicline or other investigational drug testing effects on cognition in schizophrenia o Clozapine (atypical antipsychotic medication) o Sarcosine, cycloserine, serine and glycine o Stimulants (e.g. methylphenidate, dextroamphetamine, modafinil) o Tricyclic antidepressants 4. Patients who have participated in a clinical trial with repeated assessments (i.e. a single assessment is not exclusionary) with the MCCB within the last 6 months prior to randomization 5. Significant history of drug abuse disorder within the last 6 months prior to informed consent, or a positive urine drug screen at Visit 1 6. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
Test product(s)	BI 425809
dose	10 mg q.d.
method and route of administration	Tablet, Oral
Comparator product(s)	Matching placebo
dose	Not applicable

method and route of administration	Tablet, Oral
Duration of treatment	12 weeks
Statistical methods	Restricted Maximum Likelihood (REML)-based Mixed-effect Model Repeated Measures (MMRM) analysis will be used as the primary analysis for the primary efficacy endpoint of change from baseline in the MCCB neurocognitive composite score after 12 weeks of treatment. This model will include fixed effects of treatment, age stratification factor, visit, as well as the continuous fixed covariates of baseline MCCB neurocognitive composite score, change from screening to baseline MCCB neurocognitive composite score, baseline-by-visit interaction and treatment-by-visit interaction. Patient will be treated as random effect. The unstructured variance-covariance structure will be used to model the within-patient errors. For the secondary efficacy endpoint of change from baseline in the overall MCCB composite score or PANSS total score after 12 weeks of treatment, an MMRM model same as or similar to that used for the primary endpoint will be fitted. For change from baseline in SCoRS score after 12 weeks of treatment, an ANCOVA model will be fitted. Descriptive statistics and exploratory analyses will be provided for safety data and other efficacy endpoints.

FLOW CHART

Trial Periods and Procedures	Screening Period (*)	Randomized Treatment Period					End of Study
Visit	**1 Screening**	**2[1]**	**3**	**4**	**5**	**6 (e)EoT[1,2]**	**Follow-up[2]**
Weeks			**3**	**6**	**9**	**12**	**16**
"Days" from first randomized treatment	**-28 to -1**	**0 (***)**	**21**	**42**	**63**	**84**	**EoT +28**
Time window for visits	28 days	N/A	±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[13]		X[13]	X[14]
Pregnancy test[3]	X	X	X	X	X	X	
Drug screen test (urine)	X	X		X		X	
12-lead ECG[4]	X	X		X		X	X
In-/exclusion criteria	X	X					
Contact IRT	X	X	X	X	X	X	
Randomization		X					
Dispense and administer trial drug		X	X	X	X		
Termination of trial drug[5]						X	
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	
MCCB	X[7]	X		X		X	
C-SSRS[8]	X	X	X	X	X	X	X
PANSS[9]	X	X		X		X	
SCoRS[9]	X	X				X	
[redacted]		[redacted]				[redacted]	
M.I.N.I.	X						
[redacted]		[redacted]				[redacted]	
Adverse events(*****)	X	X	X	X	X	X	X
Compliance check (study drug)			X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X
CCT device and related equipment distributed (if needed); patient trained on CCT program	X						

Trial Periods and Procedures	Screening Period (*)	Randomized Treatment Period					End of Study
Visit	**1 Screening**	**2[1]**	**3**	**4**	**5**	**6 (e)EoT[1,2]**	**Follow-up[2]**
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"Days" from first randomized treatment	**-28 to -1**	**0 (***)**	**21**	**42**	**63**	**84**	**EoT +28**
Time window for visits	28 days	N/A	±3 days	±3 days	±3 days	+3 days	+7 days
CCT run-in (2 weeks)[12]	X						
CCT compliance check	X	X	X	X	X	X	
CCT progress reviewed and re-training/reminders to patient as needed	X	X	X	X	X		
CCT device and related equipment collected from patient (if applicable)						X	
Completion of patient participation (****)							X

(*) The procedures for screening can occur on more than one day during the screening period. All procedures for screening (Visit 1) must be performed within 28 days prior to first drug administration (Visit 2) unless cannabis re-testing is performed (see below); for this reason, CCT run-in should preferably start within 7 days of written informed consent signed (enrolment). In addition, it is recommended that as many of the screening procedures as possible be assessed prior to start of CCT run-in so that patients not meeting eligibility criteria will not begin CCT; for this reason, screening laboratory samples should be collected as soon as possible following enrolment.

If cannabis re-testing per exclusion criterion 24 is performed, an extension of the screening period of up to 10 days (for total 38 days) is allowed; if randomization (date of first drug administration) cannot be performed within 38 days then the patient may instead be re-screened if allowed based on discussion between investigator and sponsor.

(**) 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 period once after discussion between investigator and sponsor. The patient who will be re-screened needs to be re-consented.

(***) Day of randomization/day of first intake of study medication.

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

(*****) After the Follow-up Visit (=individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware and only via the BI SAE form, please see Section 5.2.6.2.

[1] Study procedures for Visit 2 and (e)EoT Visit can be split into 2 sequential days (i.e. consecutive calendar days), in which case: the [redacted], MCCB [redacted] should be performed on the first day (for Visit 2, this should preferably be done within 7 days after patient completes the CCT run-in); the other neuropsychological assessments (i.e. PANSS, SCoRS, [redacted]) should be performed on the second day (for Visit 2, this would be day of first study drug intake).

[2] An early End of Treatment (eEoT) Visit, as well as a Follow-up Visit, should be performed for any patient who discontinues study medication prematurely; the eEoT Visit should be completed as soon as possible, and within 7 days, after study medication is stopped.

[3] Women of childbearing potential must perform urine (dipstick) pregnancy test at the visits indicated, or more frequently if required by local regulation. The urine dipstick test will be completed locally on-site using kits provided by central lab. In the event of a positive urine pregnancy test, a serum pregnancy test will be performed by the central lab for confirmation. For further details instructions, see Section 6.2.1 and Section 6.2.2.

[4] ECGs will be recorded for at least 10-second duration after the subjects have rested for at least 5 minutes in a supine position and prior to lab sampling.
[5] The last dose of study medication should be taken on the day before the EoT Visit. In case the EoT Visit is split into 2 sequential days (i.e. 2 consecutive calendar days), the last dose of study medication should be taken on the day before the first day of the split visit.
[redacted]
The screening MCCB assessment must be done before start of CCT run-in and at least 12 days prior to the baseline MCCB assessment at Visit 2.
[8] C-SSRS 'Baseline / Screening' version will be done at Visit 1; C-SSRS 'Since Last Visit' version will be done at all other visits.
[9] Study partner interview is needed for SCoRS and PANSS ratings. In-person ratings are preferred whenever possible, however, telephone interview is acceptable. Where approved locally, the patient and study partner interviews for SCoRS and PANSS assessments will be audio recorded for Quality Control purposes.
[redacted]
[12] Preferably within 7 days after written informed consent signed (enrolment), patients that meet eligibility criteria (according to available information) will begin the CCT run-in; this will be considered day 1 of the CCT run-in. During the screening period, once eligibility based on CCT run-in is established, the patient should not complete any further CCT until they are randomized to the treatment period. Note for re-screened patients: If CCT run-in compliance is confirmed but patient is a screen failure for another reason and is later re-screened, then the CCT run-in should not be repeated during re-screening.
[13] Any hemoglobin decrease >20 g/L (2 g/dL) since baseline (Visit 2) or leading to symptoms of anemia (e.g. dyspnea, dizziness, etc) will require safety follow-up with safety lab at the next visit(s), or earlier if considered necessary by the investigator.
[14] All patients with hemoglobin drop below 100 g/L (10 g/dL) or absolute decrease >20 g/L (2 g/dL) since baseline (Visit 2) will need to be followed up post-end of study until value returns to baseline/normal value, or resolution (per investigator's judgement).

For potential modifications of trial conduct in case of restrictions due to COVID-19, please refer to Section 4.1.4, Section 6.2, Section 8.2 and Section 10.5.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
AUC	Area under the Curve
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
CCT	Computerized Cognitive Training
[redacted]	[redacted]
CI	Confidence Interval
CIAS	Cognitive Impairment Associated with Schizophrenia
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicidal Severity Rating Scale
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Case Report Form, electronic
eDC	Electronic Data Capture
eEoT	Early End of Treatment
EoT	End of Treatment
FAS	Full Analysis Set
GLYT1	Glycine Transporter 1
Hb	Hemoglobin
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ICH-GCP	ICH Harmonized Tripartite Guideline for Good Clinical Practice
ICH M3 (R2)	Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
IPDs	Important Protocol Deviations
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File

LAI	Long-Acting Injectable
LPLT	Last Patient Last Treatment
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed-effect Model Repeated Measures
M.I.N.I.	Mini-International Neuropsychiatric Interview
NOAEL	No-observed-adverse-effect level
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetics
PPS	Per-Protocol Set
PoC	Proof of Concept
[redacted]	[redacted]
q.d.	quaque die (once a day)
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RS	Randomized Set
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCoRS	Schizophrenia Cognition Rating Scale
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Schizophrenia is a serious mental illness that is chronic and disabling. It has a lifetime prevalence of approximately 1%, with almost equal distribution worldwide and comparable incidence between men and women.

Schizophrenia is a heterogeneous syndrome and symptoms are clustered into positive, negative and cognitive impairments.

Cognitive impairments are a core feature of schizophrenia and have been shown to be a major determinant of poor functional outcome. 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). Meta-analyses of schizophrenia studies with neurocognitive assessments reported an overall mean decrement of at least one standard deviation in cognitive performance compared to community controls (R15-3853; R15-3854) and is comparable or greater than the effect sizes reported for moderate to severe traumatic brain injury (R15-3852).

Existing treatment options for schizophrenia (i.e. antipsychotics) are primarily efficacious in treating positive symptoms, however demonstrated only mild beneficial effects on cognition in schizophrenia (R15-5596; R15-5580). Antipsychotics also adversely affect some aspects of cognitive function, such as processing speed (R15-5595). So far, no drug has been approved for the treatment of Cognitive Impairment Associated with Schizophrenia (CIAS).

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 unmet medical need and drives developing novel treatments for CIAS.

It has been long hypothesized that deficits in glutamatergic signaling may underlie schizophrenia, including negative and cognitive symptoms (R13-4521). Various glutamatergic transmission-enhancing agents have been tested for the treatment of negative symptoms and/or cognitive impairments in patients with schizophrenia. Targets have included NMDA receptor co-factor glycine site, including agonists D-glycine, D-serine, and partial agonist D-cycloserine, as well as glycine transporter inhibitors, such as sarcosine and bitopertin, however previous studies have produced inconsistent results. Most of these studies were of a small sample size, making interpretation of data difficult (R15-5877; R15-5838; R15-5584; R15-5615; R15-5578; R15-5639; R13-4524; R13-4448; R15-5616). Also, pharmaceutical industry-sponsored studies with bitopertin (a glycine reuptake inhibitor) failed to separate from placebo in the pivotal program to treat negative symptoms of schizophrenia (R14-4313; R15-1273) despite a positive signal in Phase II (R15-1266).

BI 425809 works via the same mechanism as bitopertin, therefore hypotheses on bitopertin failures have been carefully evaluated in this project. Measures have been taken to address

the perceived failures including a different patient group and better control over the conduct of cognitive test batteries. One of the hypothesized reasons for bitopertin failure was lack of environmental cognitive stimulation, which is beneficial to learning as brain plasticity is activity-dependent and responds to environmental demands. However, cognitive stimulation is often absent in the lives of patients with schizophrenia (R18-1592). The current trial will test this hypothesis by providing standardized background cognitive stimulation via adjunctive Computerized Cognitive Training (CCT).

Therapeutic approaches towards CIAS frequently include various forms of psychotherapy and, increasingly, some form of cognitive remediation or cognitive training for which many approaches exist, both computerized and non-computerized (R16-2165; R16-2208). However, while some meta-analyses suggest that cognitive remediation may be able to improve cognitive abilities with a moderate but stable improvement compared to the control groups (average effect size 0.45), the studies included in this analyses are highly diverse and do not allow a clear conclusion as to what extent of treatment effect was achieved by which component of therapy (R16-2166). This is particularly true for cognitive training delivered via a computer at home, without an intervention of a therapist. Nevertheless, it is hypothesized that cognitive training may lead to a stimulation of the brain, which could result in a change in neuroplasticity.

As stated previously, no pharmacological treatment of CIAS exists to date. There has been a long-standing debate as to whether a pharmacological treatment may exert its full efficacy only when given to a patient who has a low degree of stimulation while receiving pharmacological treatment. Cognitive training may provide such stimulation as summarized above. In order to reduce bias by cognitive training provided by individuals and to allow for a certain level of standardization in the study, computerized cognitive training will be used in this study. Provided as training in home settings will make it more easily disseminated to special populations that otherwise may have difficulty accessing traditional cognitive training programs (R18-1594). At-home adjunctive CCT will be used in this study to provide background cognitive stimulation to patients treated with BI 425809.

1.2 DRUG PROFILE

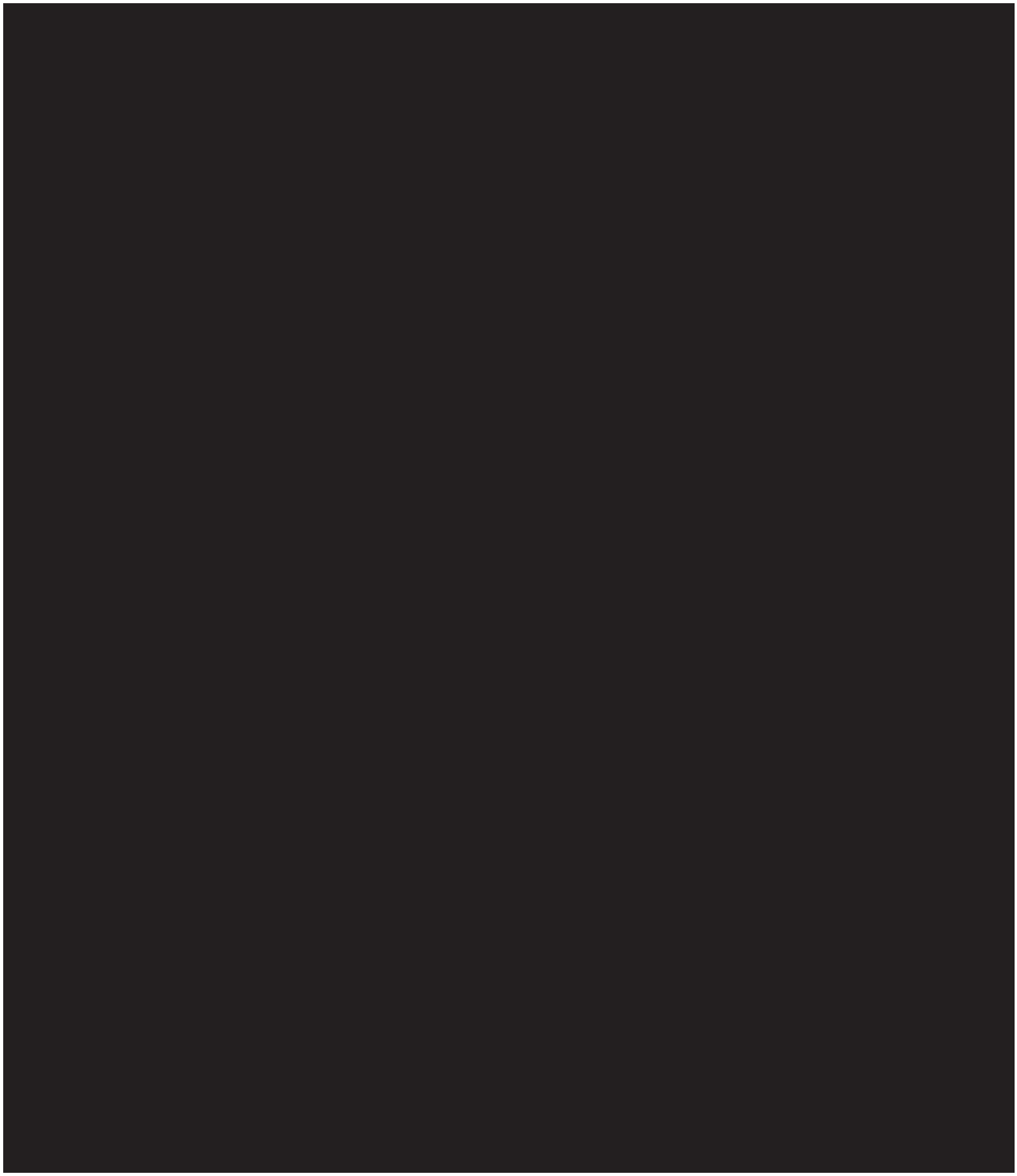
BI 425809 is a potent and selective inhibitor of the Glycine Transporter 1 (GLYT1) and, as such, increases the concentration of the NMDA receptor co-activator glycine in the synaptic cleft. *In vivo* proof-of-mechanism (i.e. indirect target engagement in the brain) was demonstrated by a dose-dependent increase of glycine in Cerebrospinal Fluid (CSF), both in rats (U13-2547) and humans (c03724403-01).

Enhancing glutamatergic neurotransmission is believed to improve brain plasticity (also referred to as neuroplasticity) which is essential for learning and memory. Indeed, pre-clinical studies with BI 425809 have demonstrated pro-cognitive properties in relevant animal models of learning and memory. It is therefore expected that treatment with BI 425809 has the potential to improve CIAS.

A comprehensive package of safety pharmacology, genetic toxicology, fertility and early embryonic development, embryo-foetal development, and repeat-dose toxicology studies has

been conducted with BI 425809. The studies support clinical trials of chronic long-term administration in adults, including women of childbearing potential (WOCBP).

Major human metabolites of BI 425809, M530 (BI 758790) and M232 (BI 761036), do not show relevant activity on GLYT1 and Glycine Transporter 2, nor against other off-targets tested. M530 and M232 have been evaluated in non-clinical studies with no evidence of pharmacological activity, genotoxicity, effects on embryo-foetal development, or adverse effects in repeat-dose toxicity.



For a more detailed description of the BI 425809 drug profile please refer to the current Investigator's Brochure (IB) (c02155957) which is included in the ISF.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Intact cognition is essential for everyday living. Cognitive impairment is a core feature of schizophrenia (R14-3766). In fact, CIAS has been shown to be a major determinant of poor functional outcome (R15-0570, R15-0567). Thus treatment of CIAS is a high unmet medical need.

Neuroplasticity, which refers to the brain's ability to acquire and store new information, is activity dependent and responds to environmental demands. Environmental cognitive stimulation conducive to learning is often absent in the lives of patients with schizophrenia (R18-1592). It was hypothesized that efficacy of compounds targeting cognition in patients with schizophrenia may be augmented by providing environmental cognitive stimulation (P17-11122). Cognitive training employing exercises engaging specific cognitive domains is an optimal tool to provide environmental cognitive stimulation, with more standardized delivery than various in-person psychosocial training. Moreover, cognitive training can be administered outside of the clinic/hospital in a computerized form known as CCT. This training can also be monitored remotely by clinicians to ensure adherence to the training.

As a strategy to enhance neuroplasticity and thereby optimize performance of compromised cognitive function in patients with schizophrenia, this study will employ CCT as an enrichment strategy adjunctive to the 12-week treatment with BI 425809. The study is designed to show superiority of BI 425809 over placebo in patients on a background of CCT.

1.4 BENEFIT - RISK ASSESSMENT

This is a Phase II Proof of Concept (PoC) study. In this study, efficacy and safety of the potential pro-cognitive medication BI 425809 on a background of cognitive stimulation will be tested in patients with CIAS.

Background cognitive stimulation will be provided using CCT outside of the clinic/hospital. A meta-analysis showed that cognitive remediation therapy, including computerized interventions in combination with other treatment modalities, such as psychotherapy and pharmacological treatment, may have a positive impact on cognition in patients with schizophrenia (R16-2166); however, the benefit of CCT alone without involvement of a psychotherapist is uncertain. The CCT program will encourage patients to regularly engage in exercises that will increase background cognitive stimulation. It is hypothesized that the beneficial impact on cognition in patients on active treatment with BI 425809 will be further enhanced as a result of the increased cognitive activity achieved through CCT.

As in other clinical trials, participation in this study may be associated with potential risks derived from administration of an investigational drug and/or from trial-related procedures. BI 425908 has been tested in 12 Phase I studies assessing safety, tolerability, pharmacokinetics (PK) and DDIs in healthy volunteers (male and female) and in two Phase II studies in patients. Study 1346-0009 tested 12-week treatment with BI 425809 in patients with schizophrenia and study 1346-0023 in patients with Alzheimer's disease. The potential risks and measures to minimize these risks that may potentially arise from administration of the study drug and/or from trial-related procedures (e.g. in-/exclusion criteria, restrictions, restricted medications, safety monitoring) are described below.

Drug-related risks and safety measures

The overall safety profile of BI 425809 is outlined in the current IB (c02155957).

Based on non-clinical toxicology data, Phase I trials in healthy volunteers and Phase II studies in patients with schizophrenia and Alzheimer's disease, BI 425809 is assessed to be generally safe and well-tolerated. The most common AEs reported more frequently for BI 425809 than placebo were were CNS-related (particularly headache, dizziness and somnolence) or GI-related (particularly nausea and vomiting), and were typically mild to moderate and transient.

Visual disturbances such as flashes of light or blurred vision were reported as adverse events in Phase I healthy volunteers studies, but these events were reported infrequently (approximately 2% of study participants) in the Phase II study in patients diagnosed with schizophrenia (c02155957). These effects are understood to be mostly mild to moderate and transient. Please refer to Section 5.2.6.2 for further details on monitoring, reporting and follow-up of any unusual visual perception that patients may experience during this study.

In longer-term studies, BI 425809 was associated with a dose-dependent decrease in Hb: in the 12-week Phase II study in patients with schizophrenia administration of the 10 mg dose resulted in a decrease of 3.3 g/L (-2.3%) at last value on treatment, while administration of

the 25 mg dose resulted in a decrease of 4.5 g/L (-3.2%) (c02155957). No clear decrease in Hb was seen in BI 425809-treated subjects compared to placebo in Phase I trials of short treatment duration. Decreased Hb is also considered to be a potential risk based on preclinical data and class effect, as GLYT1 is present on erythrocyte precursors in the bone marrow and on circulating reticulocytes and glycine is required for Hb synthesis.

Patients with Hb less than 120 g/L (12g/dL) in men or 115g/L (11.5g/dL) in women will be excluded from participation in this study. Hb will also be monitored through safety laboratory tests and additional reflex testing will be done for patients with ≥20g/L (>2g/dL) decrease in Hb since baseline as described in Table 5.2.3: 1. Patients will be withdrawn from the study treatment if: Hb level is <100 g/L (10 g/dL) AND absolute drop of >20 g/L (2 g/dL) compared to baseline (Visit 2); **or** if the subject develops anemia with symptoms of anemia such as dizziness, fatigue, pallor, shortness of breath, etc as determined by the investigator.

Results of DDI studies showed that co-administration with a strong CYP3A inhibitor increased the total exposure of BI 425809 significantly, while exposure of BI 425809 was decreased in presence of a strong CYP3A4 inducer. Therefore, concomitant use of strong and moderate inhibitors or inducers of CYP3A4 should be avoided.

Placebo risks and risks of stopping study drug

There is currently no approved medication indicated for treatment of cognitive impairment in schizophrenia. Therefore, 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, remain on antipsychotic and other psychotropic medications throughout the study. Moreover, all patients will complete adjunctive CCT as described above.

According to the medication assignment planned in this trial, 50% of the patients will receive BI 425809 and 50% of patients will be assigned to placebo. Inclusion criteria imply that patients enrolled in this clinical trial should be in stable clinical status and on stable doses of antipsychotic and concomitant psychotropic medications. Assignment to the placebo arm or stopping the study drug during the treatment period is not associated with a higher risk since patients remain on their stable treatment regimen with antipsychotics. 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 any necessary actions taken according to stopping criteria.

Although this is an experimental drug at an early stage of clinical development 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.

Study procedure risks

The patients may feel discomfort during some of the study procedures, among other study procedure risks, such as blood draw. The potential risks of a blood draw include fainting and pain, bruising, swelling, or rarely infection where the needle is inserted. In rare cases a nerve may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch and persistent pain.

We do not anticipate any risks associated with CCT. The weekly training duration is split up into short sessions (i.e. it is recommended that patients complete approximately 2.5 hours of CCT per week divided into 3-5 sessions of 30-50 minutes duration) to avoid strain caused by prolonged use of a personal computer (laptop/desktop) or tablet device.

In summary, results of this study will determine whether benefit of treatment with potential pharmacotherapies targeting modulation of neuroplasticity would increase with cognitive stimulation through adjunctive CCT in patients with schizophrenia. This is of utmost importance as cognitive stimulation is low or even absent in the lives of patients. It was indeed hypothesized as one of the reasons for past failures during development of new medications to treat CIAS. Since there is currently no approved pharmacotherapy to improve CIAS, finding an effective treatment represents a high unmet medical need. Considering the chronic and severe disease burden of CIAS, and moreover the potential additional favorable effect of adjunctive CCT on cognition in all study patients, the potential therapeutic benefits are assessed to outweigh the currently understood potential risks of the treatment and/or trial-related procedures.

Other risks

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 Columbia Suicidal Severity Rating Scale (C-SSRS). No signal was observed for suicidal ideation or behavior in patient studies of 12 weeks treatment duration.

Although rare, a potential for drug-induced liver injury (DILI) 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 5.2.6, adverse events of special interest (AESI).

Overall, the risk for patients with schizophrenia participating in BI 425809 CIAS clinical trials is considered increased in light of Coronavirus Disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), due to the need for the study participant to leave his/her home, higher prevalence of medical comorbidities such as diabetes, COPD, and cardiovascular disease that may increase the risk of developing COVID-19 related complications and due to potential decrease in Hb after treatment with BI 425809.

Therefore, appropriate risk minimization measures will be taken in accordance with the public health precautions implemented in the country where the study will be conducted (e.g. minimizing time at the clinic, replacement of physical visits with remote visits where possible, minimizing the use of public transportation to the site). In the event of restriction to visit the investigator site, certain procedures can be done remotely, and local labs can be used instead of central lab, as described in Section 10.5. These changes are meant to keep the integrity of the trial and they will not affect the benefit-risk of BI 425809. Considering the risk, patients with known active SARS-CoV-2 infection within 30 days prior to randomization will be excluded from participation in this study. Also, the study drug should be discontinued if the patient experiences severe or serious symptomatic infection with SARS-CoV-2 (see Section 3.3.4.1).

The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the trial. Boehringer Ingelheim (BI) as the sponsor, where required, will support the investigator in their decision making. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the patient.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this Phase II exploratory trial is to provide PoC data to assess the effect on cognition of oral once daily administration of BI 425809 given for 12 weeks in patients with schizophrenia on stable antipsychotic treatment and adjunctive CCT.

2.1.2 Primary endpoint(s)

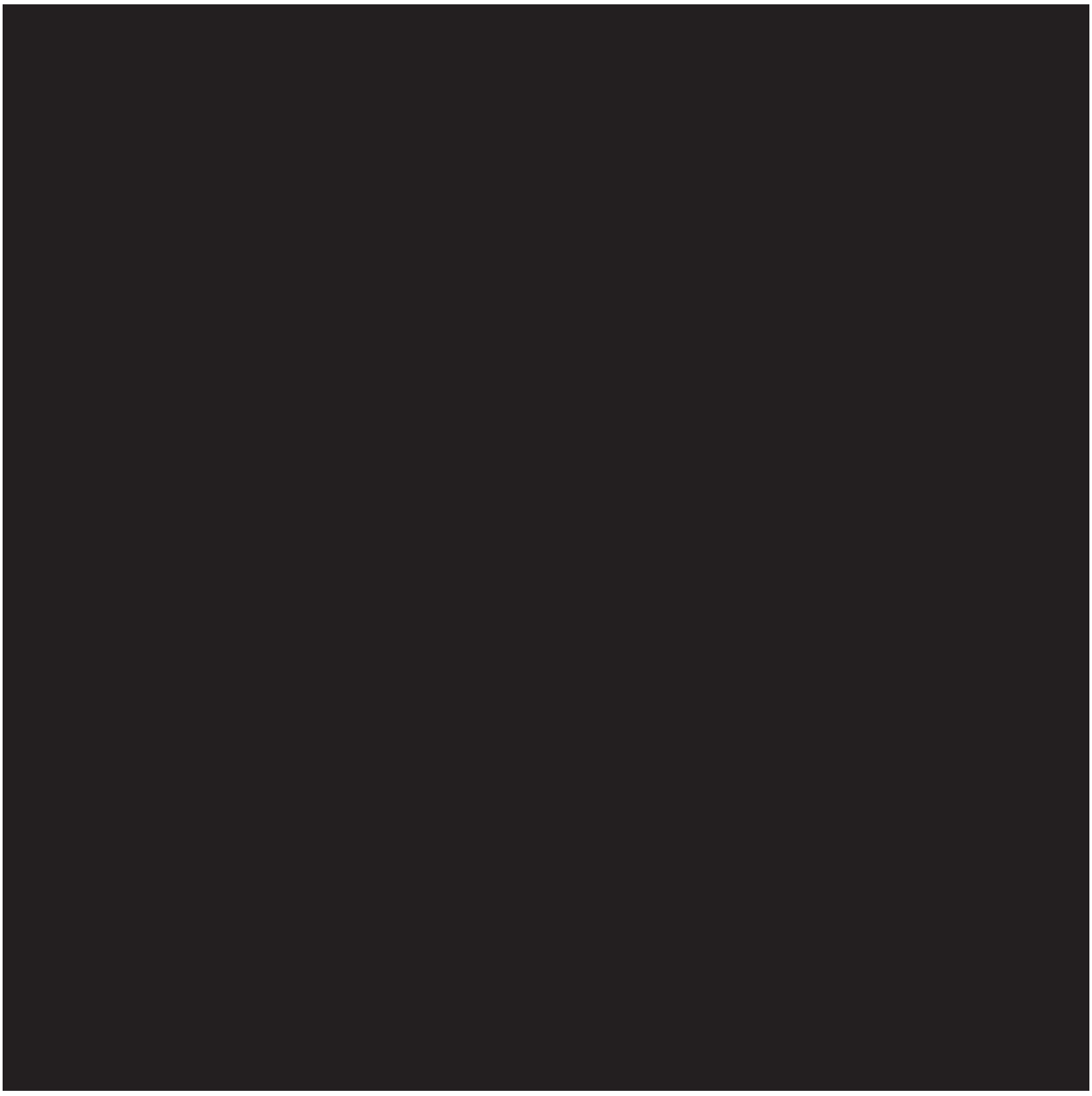
Change from baseline in neurocognitive function as measured by the neurocognitive composite score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 12 weeks of treatment is the primary efficacy endpoint.

MCCB neurocognitive composite score (including all MCCB domains except Social Cognition) was selected because it was found to have greater sensitivity to treatment effect in previous studies in the same population (R18-1873).

2.1.3 Secondary endpoint(s)

The secondary endpoints of efficacy and safety are as follows:

- Change from baseline in cognitive function as measured by the overall MCCB composite score (including social cognition) after 12 weeks of treatment
- Change from baseline in the effect of cognitive deficit on day-to-day functioning as measured by SCoRS total score after 12 weeks of treatment
- Change from baseline in Positive and Negative Syndrome Scale (PANSS) total score after 12 weeks of treatment
- Percentage of patients with (S)AEs (including clinically relevant abnormalities of physical examination, vital signs, ECG test and laboratory tests)



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The overall trial design is as follows:

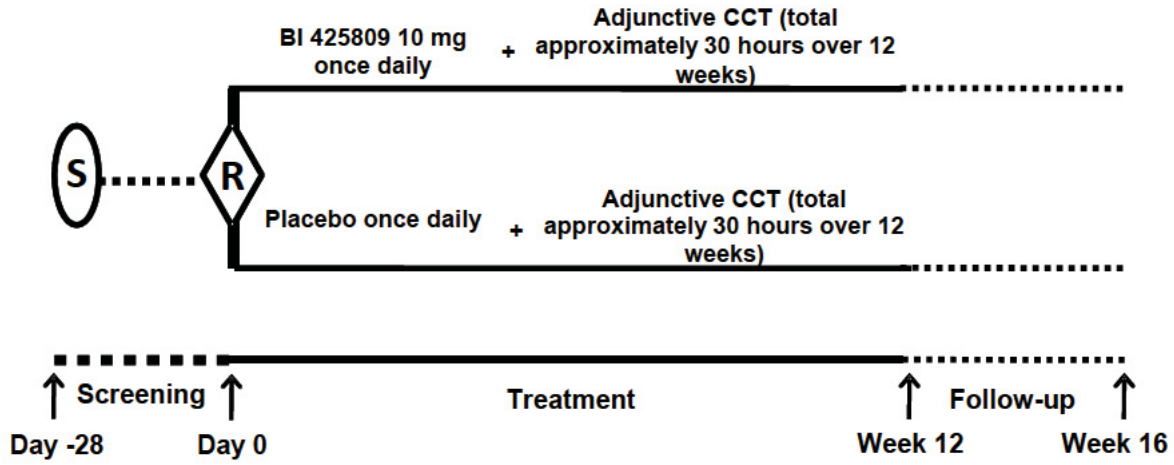


Figure 3.1:1 Trial design

This is a 12-week, multi-center, multi-national, randomized, double-blind, placebo controlled parallel group trial in patients with schizophrenia. In total, 200 patients with schizophrenia on stable antipsychotic treatment who meet the eligibility criteria are planned to be randomized into this trial.

Patients are enrolled in the trial once informed consent has been signed. Patients will undergo CCT run-in for two weeks during the screening period. Patients compliant with the CCT run-in procedure and otherwise suitable after screening will be randomized to the 12-week treatment period assigned at a ratio of 1:1 to one of two arms:

- BI 425809 10 mg once daily + adjunctive CCT (total approximately 30 hours over 12 weeks)
- Placebo once daily + adjunctive CCT (total approximately 30 hours over 12 weeks)

The randomized treatment will be double blind.

Patients will be stratified by age (age 18-40 and age 41-50) via Interactive Response Technology (IRT) to control and balance the possible prognostic effect of age.

After completion of the treatment period, or following early discontinuation of trial medication at any time point, patients will complete the Follow-up Visit to evaluate safety 4 weeks after last intake of trial medication. Safety may be evaluated for an appropriately

longer time, in the investigator's opinion, in case of unresolved AEs. Individual patient participation is concluded when the patient has completed their last planned visit.

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 and adjunctive CCT. The primary analysis of efficacy is planned after 12 weeks of treatment (refer to Section 5.7 for appropriateness of treatment duration). The 4 weeks (+7-day window) post-treatment Follow-up Visit is considered to be sufficient to evaluate the pharmacodynamic effect of BI 425809 after discontinuation and allow for assessment of reversibility of any unexpected side-effects. Details of the statistical approach and sample size justification are given in Section 7.

There is currently no approved medication indicated for treatment of CIAS and therefore, a placebo control group is being used in this study design. However, all patients will complete adjunctive CCT which has emerged as a non-pharmacological approach to improve cognitive impairments in patients with mental illness. It should be noted that all patients, including those randomized to the placebo group, are permitted to remain on other antipsychotic and psychotropic medications, within the eligibility criteria. The risk to the control group is discussed in Section 1.4.

This study includes CCT run-in for two weeks during the screening period. The intention of this CCT run-in is to evaluate patient compliance with an at-home (i.e. completed by the patient independently, most likely at home, without clinician intervention) CCT program prior to randomization, in order to minimize the number of patients randomized at Visit 2 who will not be compliant with at-home CCT during the treatment period. See further Section 4.3 and Section 6.2.1.

3.3 SELECTION OF TRIAL POPULATION

It is planned that around 58 trial centres in 6 countries will be participating in this trial and a sufficient number of patients will be screened for the trial to ensure that 200 patients are randomized to trial treatment.

It is expected that approximately 5 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 15 patients per site must be obtained from the Clinical Trial Leader (CTL). 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 sites once a sufficient number of patients has been screened. Investigators will be notified

about screening completion and will then not be allowed to screen additional patients for this trial.

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

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

It was decided that patients in this study should be maximum 50 years of age, as neuroplasticity (i.e. ability of the brain to change during life by acquiring, storing and re-using information) declines with age as well as with duration of the illness and treatment with antipsychotics. If BI 425809 is shown to be efficacious in this age group, it is planned to conduct additional studies to explore efficacy in patients over 50 years of age.

3.3.1 Main diagnosis for trial entry

Only patients with established Schizophrenia (as per Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (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 for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP) and local legislation prior to admission to the trial.

2. Male or female patients 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[1] prior to randomization
    - Psychiatrically stable without symptom exacerbation within 3 months prior to randomization
    - PANSS score ≤ 5 on positive items P1, P3-P7 and ≤ 4 on positive item P2 at Visit 1, and confirmed at Visit 2

[1] Hospitalization for social management and/or day hospital programs within this time are acceptable.

4. Patients must be on stable antipsychotic treatment; also, current antipsychotic medications and concomitant anticholinergics, antiepileptics, lithium and allowed antidepressants must meet the criteria below:
    - Patients must take 1 and may take up to 2 antipsychotics (typical and/or atypical), except for clozapine (see Section 3.3.3)
    - Patients must be stable on current antipsychotics, anticholinergics, antiepileptics, lithium and allowed antidepressants for at least 3 months prior to randomization and be on current dose for at least 30 days prior to randomization
        - Patients on Long-Acting Injectable (LAI) antipsychotics should be on the same medication and dose for at least 3 months prior to randomization

5. Women of childbearing potential (WOCBP)[2] must be ready and able to use highly effective methods of birth control per Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3 (R2)) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in Section 4.2.2.3. Such methods should be used throughout the trial, and for a period of at least 35 days after last trial drug intake, and the patient must agree to periodic pregnancy testing during participation in the trial.

6. Patients must demonstrate their ability to properly use the CCT device and program, as well as be compliant with CCT run-in (defined as completing at least 2 hours per week for two weeks, totalling 4 hours CCT, during the screening period)[3].

7. Patients must be able to comply with all protocol procedures, in the investigator's opinion.

8. Patients must have a study partner who will preferably be consistent throughout the study. It is recommended that the study partner should interact (in-person or telephone) with the subject at least 2 times a week.

3.3.3 Exclusion criteria

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

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

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[2] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[3] If target compliance is not met but the investigator believes the patient will be compliant during the treatment period, then the investigator should contact the CTM or CTL prior to randomization and a documented discussion should take place to determine whether the patient can be randomized (see Section 4.3).

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 with a history of participating in any formal cognitive remediation program for 10 or more training sessions.

5. Patients who were treated with any of the following medications within the last 6 months prior to randomization:
    - Bitopertin, BI 409306, encenicline or other investigational drug testing effects on cognition in schizophrenia
    - Clozapine (atypical antipsychotic medication)
    - Sarcosine, cycloserine, serine and glycine
    - Stimulants (e.g. methylphenidate, dextroamphetamine, modafinil)
    - Tricyclic antidepressants

6. Patients receiving any other investigational drug (other than a potential cognitive enhancing drug) within 30 days or 6 half-lives (whichever is longer) prior to randomization. For investigational LAI antipsychotics, the last injection must be at least 3 months or two administration cycles (i.e. 6 months if administration is every 3 months) prior to randomization, whichever is longer.

7. Patients who have participated in a clinical trial with repeated assessments (i.e. a single assessment is not exclusionary) with the MATRICS Consensus Cognitive Battery (MCCB) within the last 6 months prior to randomization.

8. Patients who required a change in ongoing benzodiazepine or sleep medication dose or regimen within the last 30 days prior to randomization.

9. Use of systemic steroids within 30 days prior to randomization.

10. 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.

11. 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).

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

13. Patients who have received electroconvulsive therapy (ECT) within 6 months prior to randomization or repeated courses of ECT within the past 2 years.

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 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. Any of the following, in the judgment of the investigator:
    - Clinically significant finding of the physical examination, vital signs (including blood pressure (BP) and pulse rate (PR)), ECG or laboratory value (as measured by the central laboratory) that would jeopardize the patient´s safety while participating in the trial or their capability to participate in the trial.
    - 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 or capability to participate in the trial.
    - Significant or unstable physical condition that may require change in medication or hospitalization that would impact cognitive function, or planned elective surgery requiring general anesthesia during the study period.
    - Patients for which cognitive or other impairment (including severe hearing impairment) or symptom severity compromises the ability to perform the CCT or assessments related to cognitive outcome measures.

17. Severe renal impairment defined as an eGFR < 30mL/min/1.73m² in the Visit 1 central lab report.

18. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 times upper limit of normal as determined in the Visit 1 central lab report.

19. Known history of HIV infection based on review of medical history and/or a positive result for ongoing Hepatitis B or C infection on the Visit 1 central lab report.

20. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.

21. Hb less than 120 g/L (12g/dL) in men or 115 g/L (11.5g/dL) in women at Visit 1.

22. History of hemoglobinopathy such as thalassemia major or sickle-cell anemia.

23. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

24. Significant history of drug abuse disorder within the last 6 months prior to informed consent (including alcohol, as defined in DSM-5-substance use disorder or in the opinion of the investigator), or a positive urine drug screen at Visit 1. For a list of drugs assessed in the urine drug screen, please refer to Table 5.2.3: 1. Note: Patients testing positive for cannabis on urine drug screen at Visit 1 may be re-tested once if there is a reasonable explanation and expectation that the patient will not test positive again on re-test, and at the discretion of the investigator.

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

26. Patient who did not make an effortful attempt to complete the cognition battery at Visit 1 in the clinical judgement of the investigator.

27. Patients that previously received treatment in any study with BI 425809.

28. Patients with an allergy to BI 425809 and/or any of the excipients (including lactose) or placebo ingredients. A list of BI 425809 and placebo ingredients will be provided in the ISF.

29. Patients with known active infection with SARS-CoV-2 within the last 30 days prior to randomization.

3.3.4 Withdrawal of patients from therapy or assessments

Every effort should be made to keep the randomized patients in the trial, if possible.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and electronic Case Report Form (eCRF). If the reason for discontinuation is death, this should be reported on the Serious Adverse Event (SAE) form as well, regardless of causal relationship.

3.3.4.1 Withdrawal from trial treatment

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

- The patient wants to withdraw from trial treatment or study participation, without the need to justify the decision
- The patient needs to take concomitant drugs that interfere with the investigational product or are restricted (see Section 4.2.2.1)
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy)
    - 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 5.2.6.2.

- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future
- 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)
- Hb level <100 g/L (10 g/dL) AND absolute drop of >20 g/L (2 g/dL) since baseline (Visit 2); **or**
  The subject develops anemia with symptoms of anemia such as dizziness, fatigue, pallor, shortness of breath, etc as determined by the investigator
- The patient needs to stop all current antipsychotic medications
- The patient's disease state dramatically worsens, in clinical judgement of investigator
- The patient experiences severe or serious symptomatic infection with SARS-CoV-2

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 from trial treatment (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

Patients who discontinue or withdraw from the study after randomization (Visit 2) will be considered as "early discontinuations". 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.

Patients who drop out prior to randomization will be considered Screening Failures. They will be recorded as Screening Failures in the 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 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient. See further Section 3.3.4.1 above.

3.3.4.3 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 ICH-GCP, the trial protocol, or the contract impairing 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 INVESTIGATIONAL TREATMENTS

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

Eligible patients are randomly assigned to one of the double-blind treatment regimens at a ratio of 1:1 as follows:

- BI 425809 10 mg once daily for 12 weeks
- Placebo once daily for 12 weeks

All patients will receive non-pharmacological adjunctive CCT (see further Section 4.2.1).

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

The characteristics of the test product are as shown below.

Table 4.1.1: 1 Test product:

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

The characteristics of the reference product are as shown below.

Table 4.1.1: 2 Reference product:

Substance:	Placebo matching BI 425809 5 mg
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable

Posology	2-0-0 for the placebo dose group
Method and route of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

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 (150 mg per day), please refer to Section 1.2 for more details.

Based on preclinical data in animal cognition tasks, BI 425809 shows efficacy at doses which correspond to ~50% glycine increase in CSF and CSF levels of the drug in the range of 1x GLYT1 IC_{50} (see chapter 5.1.1.2 of the IB c02155957).

In the Proof of Mechanism trial (c03724403-01) demonstrating functional target engagement in healthy volunteers, the target mean increase of 50% in CSF glycine was observed after multiple dosing of 10 mg BI 425809 indicating that this dose level generates sufficient drug exposure and glycine increases in the brain that are expected to lead to improvement of the cognitive abilities in human.

Therefore, based on the preclinical data and data from the Proof of Mechanism Trial, 10 mg of BI 425809 was chosen as the dose level to be investigated in the present study.

4.1.3 Method of assigning patients to treatment groups

During Visit 2, eligible patients will be randomized to receive BI 425809 10 mg q.d. or placebo in a 1:1 ratio according to a randomization plan. The study drug assignment will occur in a blinded fashion via IRT. All patients will complete adjunctive CCT for the duration of the treatment period (see further Section 4.1.1).

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, Visit 3, Visit 4 and Visit 5. 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 Visit 2, Visit 3, Visit 4 and Visit 5, patients will receive one treatment kit containing supplies for a total of 28 days (21 treatment days plus 7 days reserve).

The first dose of study medication will be taken at the end of Visit 2 under supervision of the investigator or site staff. For patients that complete the treatment period, the last dose of study medication should be taken on the day before the EoT Visit. In case the EoT Visit is split into 2 sequential days (i.e. 2 consecutive calendar days), the last dose of study

medication should be taken on the day before the first day of the split visit. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day.

Patients should be instructed not to take their trial medication in the morning before Visit 3, Visit 4 and Visit 5, as patients will be dosed at the site [redacted]). Patients should also be instructed not to take their trial medication in the morning before Visit 6/End of Treatment (EoT) Visit/early End of Treatment (eEoT) Visit, [redacted]

Otherwise, patients should be instructed to take two tablets orally with water and with or without food in the morning. 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.

A dose reduction of BI 425809 is not possible.

Due to the COVID-19 pandemic, there might be situations that would not allow a patient to come to the site for the study visit. If the investigator judges it as favourable and safe to continue trial medication, trial medication might be shipped from the site to the patient (for more details see Section 6.2, Section 8.2 and Section 10.5).

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 (study drug arms) until after database lock. All randomized patients will complete adjunctive CCT (see further Section 4.1.1).

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.

The randomization codes will be provided to bioanalytics prior to "last patient out" (i.e. last visit completed by the last patient) [redacted] Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator / pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be

documented in the source documents and/or appropriate eCRF page along with the date and the initials of the person who broke the code.

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

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated contract research organization (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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 Clinical Trial Manager (CTM) (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator, 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 clinical trial protocol (CTP) by the Institutional Review Board (IRB) Independent Ethics Committee (IEC),
- Availability of a signed and dated clinical trial contract between the sponsor and 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 CTP,
- Availability of the proof of a medical license for the Principal Investigator (if applicable),
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

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 warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Emergency treatments and procedures

Only patients with stable schizophrenia are included in this trial. As such, no rescue medication or emergency procedures are foreseen for this trial.

In case of worsening of schizophrenia, any treatment deemed necessary per clinical judgment can be given.

Other treatments

Throughout the duration of the trial patients should continue to take only 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.

Adjunctive Computerized Cognitive Training (CCT)

All patients in the study will complete adjunctive CCT for the duration of the 12-week treatment period (and additional CCT run-in during the screening period).

Total CCT will be approximately 30 hours spread over the 12-week treatment period. It is recommended that patients complete approximately 2.5 hours of CCT per week divided into 3-5 sessions of 30-50 minutes duration. Patients can split assigned training sessions into shorter segments, instead of completing the session as one continuous workout, however patients should be instructed that the training done during a session or segment thereof should preferably be minimum 10 minutes duration. Sessions should not exceed 1 hour of continuous training to patient fatigue.

The same program will be used to deliver CCT during both the screening and treatment period. The CCT exercises completed during the screening period (CCT run-in) will match the CCT exercises completed during the treatment period in order to most effectively serve the intention of the CCT run-in, which is to identify and exclude patients who will not be compliant with completing at-home CCT exercises. It is recognized that patients may gain some benefit from completion of CCT during the run-in period. To minimize the effect of CCT during run-in, a large variety of exercises will be delivered so that patient will have limited exposure to any one particular exercise, and all exercises will start at the lowest level of difficulty. In addition, once eligibility based on CCT run-in is established, patients should be advised to not complete any further CCT until they are randomized to the treatment period.

Selection of CCT target duration

The CCT target duration of total approximately 30 hours divided into 3-5 sessions per week is based on a meta-analysis published in 2011 (R16-2166) of cognitive remediation therapy for schizophrenia. This review examined 2,104 patients who participated in 40 different studies. The average length of administration (CCT use) was 32.2 hours over an average of 16.7 weeks. Results showed a statistically significant improvement in global cognition of moderate effect size (average 0.45). The meta-analysis included studies that used both computerized and non-computerized methods, with no difference between the two approaches.

Our goal for the CCT component of this study is not to improve cognition but to provide a moderate level of background cognitive stimulation. Based on the above-mentioned meta-analysis, it was determined that total approximately 30 hours of CCT over 12 weeks with a recommendation for 3-5 sessions per week should allow for the desired moderate level of background cognitive stimulation from the adjunctive CCT.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medications listed under the inclusion criteria (Section 3.3.2) and exclusion criteria (Section 3.3.3) are restricted during the trial period as well.

In addition, the following concomitant medication and treatment restrictions apply for the duration of the trial:

- Patients should not be on maintenance therapy with opioids (e.g. methadone, suboxone) during the trial period
- If given, olanzapine daily dose per label should not be exceeded
- Patients taking anticholinergic and antihistaminic medication should be on a stable dose not exceeding daily recommended dose per label in the country
    - Particular caution regarding the total dose should be taken for patients that are being treated with anticholinergics for various indications
- Patients should take the last dose of antihistaminic, benzodiazepine or other sedative medication no less than 8 hours before MCCB during the trial period; in case this cannot be done at a scheduled visit, then the visit should preferably (if possible) be rescheduled within the allowed visit window
- New or changes in dose and frequency of psychosocial treatments (including social skills treatment or vocational treatment, and not including cognitive remediation therapy) is not permitted during the trial period; if patients are on these treatments at randomization, this should not have been started or changed in the prior three months
- Additional (i.e. non-study) cognitive remediation therapy, cognitive behavioural therapy or cognitive training is not permitted during the study period
- Any medication that may interfere with the pro-cognitive action of BI 425809 is not permitted during the treatment period and the 4-week follow-up period, in the clinical judgment of the investigator
- Patient will not receive electroconvulsive therapy nor begin any type of traditional/complementary therapies for cognition
- CYP3A4 sensitive drugs with narrow therapeutic range (such as cyclosporine or fentanyl) are not permitted during the trial period
    - A list of CYP3A4 sensitive drugs with narrow therapeutic range will be provided in the ISF

Further notes regarding concomitant medication and treatment restrictions:

- Non-systemic use (topical, inhalation or nasal administration) of corticosteroids, antihistaminics and anticholinergics is allowed.
- The allowed CYP3A4 sensitive drugs 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)

4.2.2.2 Restrictions on diet and life style

The following are not permitted starting 7 days before the first administration of trial medication until the (e)EoT Visit:

- Grapefruit
- St. John's wort (Hypericum perforatum)
- Dietary supplements and herbal remedies that may impact cognition, in the investigator´s judgement

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 alcohol or use drugs of abuse during the study. A urine drug screen will be performed at selected study visits (see Flow Chart). For a list of drugs assessed by the urine drug screen please refer to Table 5.2.3: 1.

Patients should not enter or modify a smoking-cessation program during the conduct of the trial.

Patients should keep their usual habits throughout the study for diet and exercise, as well as nicotine, alcohol and caffeine intake.

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

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to Section 3.3.2) must use highly effective methods of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly. Such methods should be used throughout the trial, and for a period of at least 35 days after last trial drug intake.

Acceptable methods of birth control for this trial include:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm
- Complete sexual abstinence when this is in line with the preferred and usual lifestyle of the patient (note: periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception)

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 ISF.

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 shown in the formula below. Compliance will be verified by the Clinical Research Associate (CRA) authorised by the sponsor.

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

If the number of doses taken is not between 80-120%, site staff will re-train the patient and explain the importance of treatment compliance. The site should also discuss with the patient if the number of doses taken is greater than 100%, to determine the reason.

Compliance with adjunctive CCT

Total CCT will be approximately 30 hours spread over the 12-week treatment period. Optimally, patients should complete approximately 2.5 hours of CCT per week divided into 3-5 sessions of 30-50 minutes duration. Patients can split the training sessions into shorter segments during the day and throughout the week, however the training done during a session or segment thereof should preferably be minimum 10 minutes duration.

CCT compliance will be monitored on an ongoing basis by site staff (CCT coach) that should follow up with patients to discuss compliance status and provide advice and motivation as necessary. See Section 6.2 for further description of the role and responsibilities of the CCT coach.

CCT compliance during run-in (screening period)

The CCT run-in will be completed by the patient during the screening period. Patients that comply with CCT run-in will be eligible for randomization. Preferably within 7 days after written informed consent signed (enrolment), the CCT run-in will begin. The baseline MCCB assessment at Visit 2 should be done within 7 days after patient completes the CCT run-in whenever possible. This allows sufficient time for patients to complete the CCT run-in (two weeks) and for sites to receive/review the compliance results prior to Visit 2.

Target compliance for the CCT run-in is at least 2 hours per week for two weeks, totalling 4 hours, during the screening period. If target compliance is not met but the investigator believes the patient will be compliant during the treatment period, then the investigator should contact the CTM or CTL prior to randomization and a documented discussion should take place to determine whether the patient can be randomized. See further Section 6.2.1.

During the screening period, once eligibility based on CCT run-in is established, the patient should not complete any further CCT until they are randomized to the treatment period.

CCT compliance during treatment period

CCT compliance during the treatment period should also be maintained at 2-3 hours (i.e. approximately 2.5 hours) per week across 3-5 sessions. Additionally, the CCT coach will discuss compliance during regular contact (at least weekly) with patients (see further description of CCT coach role and responsibilities in Section 6.2).

Minimum compliance expectation is at least 1 hour per week throughout the trial. Any instance in which a patient completes less than 1 hour of CCT in any given week will be recorded as a protocol deviation (i.e. CCT low compliance).

Patients that do not complete any of the assigned CCT (i.e. zero sessions started) for 3 consecutive weeks or more will be recorded as a protocol deviation (i.e. CCT non-compliance).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

During the scheduled visits, the investigator or site staff will perform the evaluations by asking subjects questions or help subjects to complete the evaluations which have to be done by themselves at sites.

In some cases the investigator or site staff will ask the study partner questions in order to complete evaluations. A study partner is defined as any person who has been capable of interacting with the patient over the past week. It is recommended that the study partner should interact (in person or telephone) with the subject at least 2 times a week. If the study partner is not available for in person interview at the scheduled visit, telephone interview is acceptable. The study partner should preferably be the same person throughout the study. However, in the event that the identified study partner becomes unavailable or unwilling to provide input during the study, the patient should contact the investigator and identify a new study partner.

MATRICS Consensus Cognitive Battery (MCCB) will be used at screening (Visit 1), randomization (Visit 2/baseline), Visit 4 and (e)EoT Visit to evaluate the effects of BI 425809 on cognitive functions.

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).

The 10 tests of the MCCB with corresponding cognitive domains are listed in Table 5.1: 1 below:

Table 5.1: 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)

Test	Domain
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
Continuous Performance Test, Identical Pairs version (CPT-IP)	Attention/ Vigilance

Social cognition is distinct from non-social cognition (i.e. neurocognition), thus the MCCB neurocognitive composite score will be calculated without the Social Cognition domain. The MCCB neurocognitive composite score will be used as the primary efficacy endpoint measure for this study, while the overall MCCB composite score will be used as a secondary efficacy endpoint.

Schizophrenia Cognition Rating Scale (SCoRS) is a 20-item interview-based assessment of cognitive deficits and the degree to which they affect day-to-day functioning. 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 responses. If five or more of the 20 items are missing, the composite score will be missing (R13-2345; R16-4322).

The 20 items of the SCoRS specifically assess cognitive functioning, and 19 of these items align with the seven MCCB cognitive domains as follows:

- 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

The one additional item of the SCoRS falls within Language, which is not an MCCB domain.

The SCoRS rater integrates information from separate patient and study partner interviews to generate a total score.

SCoRS will be assessed at screening (Visit 1), randomization (Visit 2) and (e)EoT Visit.

[redacted]

[redacted]

Positive and Negative Syndrome Scale (PANSS) will be used to evaluate broad psychopathology associated with schizophrenia disease state at screening (Visit 1), randomization (Visit 2), Visit 4 and (e)EoT Visit.

The PANSS has 30 items. Each is rated from 1 to 7 points. The total factor score is the summation of the actual points for each item, leading the total score ranging from 30 to 210. (R13-5061).

[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, skin, eyes and nervous system. The physical examination will include examination of known and suspected sites of disease. A complete physical exam is also required at eEoT Visit.

Clinically relevant abnormal findings noticed from physical examination after Visit 1 assessment will be reported as (S)AEs.

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

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling, including the (e)EoT Visit and the Follow-up Visit (4 weeks after (e)EoT). This includes temperature, systolic and diastolic BP and PR (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

BP measurement can be done manually or electronically (preferably with the same device at every visit). The BP measurement can be repeated after 10 minutes rest at the discretion of the investigator (e.g. if there is reason to think the patient was anxious or under stress at the time of first measurement), in which case the second measurement should be recorded in the eCRF.

Clinically relevant abnormal findings from vital signs evaluation noticed after Visit 1 will be reported as (S)AEs.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the Flow Chart.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings on lab results after baseline safety laboratory parameters are assessed, as judged by the investigator, will be reported as AEs (please refer to Section 5.2.6).

Laboratory results of the patients will be available to the respective investigator and to the sponsor, and abnormal laboratory alerts will be sent automatically to the sites and to the sponsor within 24 hours.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the eDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor.

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 the eCRF either on baseline condition (from Visit 1 test) or on AE page (from subsequent visits test). The following lab parameters will not be determined at each study visit:

- Vitamin B12 and folate – only at Visit 1
- TSH – only at Visit 1
- Infections screen – only at Visit 1
- Prolactin – only at Visit 2 and (e)EoT

Table 5.2.3: 1 Safety laboratory tests

Category	**Test name**
Haematology	Hematocrit (Hct) Hemoglobin (Hb)* 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 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 Estimated Glomerular filtration rate (eGFR) – using the CKD-EPI equation Prolactin
Pregnancy test (females only)	Human urine chorionic gonadotropin Serum Beta hCG, Qualitative – only if human urine chorionic gonadotropin is positive

Category	Test name
Urinalysis	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH Urine creatinine
Drug screen (urine)	Cannabis Barbiturates Opiates Cocaine Amphetamines Methadone PCP
Infections screen (only at Visit 1)	Hepatitis B Surface antigen (qualitative) Hepatitis C antibodies (qualitative) Hepatitis C Vaccine (HCV) RNA – only if Hepatitis C antibodies (qualitative) is positive

*For patients with >2g/dL decrease in Hb since baseline (Visit 2), the following tests will be added: serum ferritin, serum iron, TIBC, reticulocyte index.

5.2.4 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 and prior to lab sampling. 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 (Visit 1) should be reported as baseline condition.

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

5.2.5 Other safety parameters

5.2.5.1 Assessment of disease state

PANSS will be used to evaluate the disease state. It contains seven positive symptom items, seven negative symptom items and 16 general psychopathology symptom items. Fourteen of the PANSS items require input from a study partner. A trained rater interviews the patient and the study partner, estimated to take 30-40 minutes for evaluating the subjects' disease state.

5.2.5.2 Assessment of suicidality

Suicidal risk 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 interview may be administered using a tablet device. 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 to answer all relevant questions. This assessment should be conducted early in the visit. At the conclusion of each assessment, the site will have access to the eC-SSRS results via a web-based portal. The results include 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 eC-SSRS will be administered first at screening (Visit 1) (using the 'Baseline / Screening' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to screening. The life time history of suicidal ideation and behavior will also be recorded.

After screening (Visit 1) the assessment 'since last visit' will be performed at each clinic visit ('Since Last Visit version'). The investigator is to review/consider the eC-SSRS results for plausibility and clinical relevance. Doubtful results may be repeated or results may be validated by a consulting psychiatrist. 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 (if the investigator did not administer the C-SSRS leading to the positive report), and/ or is to consult a psychiatrist if considered necessary. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.

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

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

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

Adverse event

An 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.

The following should also be recorded as an AE in the eCRF and BI 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*

*Note: If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

Regarding AEs in the context of suicidal risk assessment by C-SSRS, Section 5.2.5.2 should be adhered.

Serious adverse event

A SAE is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which 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.
- requires inpatient hospitalization or
- requires prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Regarding SAEs in the context of suicidal risk assessment by C-SSRS, Section 5.2.5.2 should be adhered.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, sub-sections "AE Collection" and "AE reporting to sponsor and timelines".

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further 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 defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above.

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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

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 (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- 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 in the eDC 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 (severity) of AEs

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

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

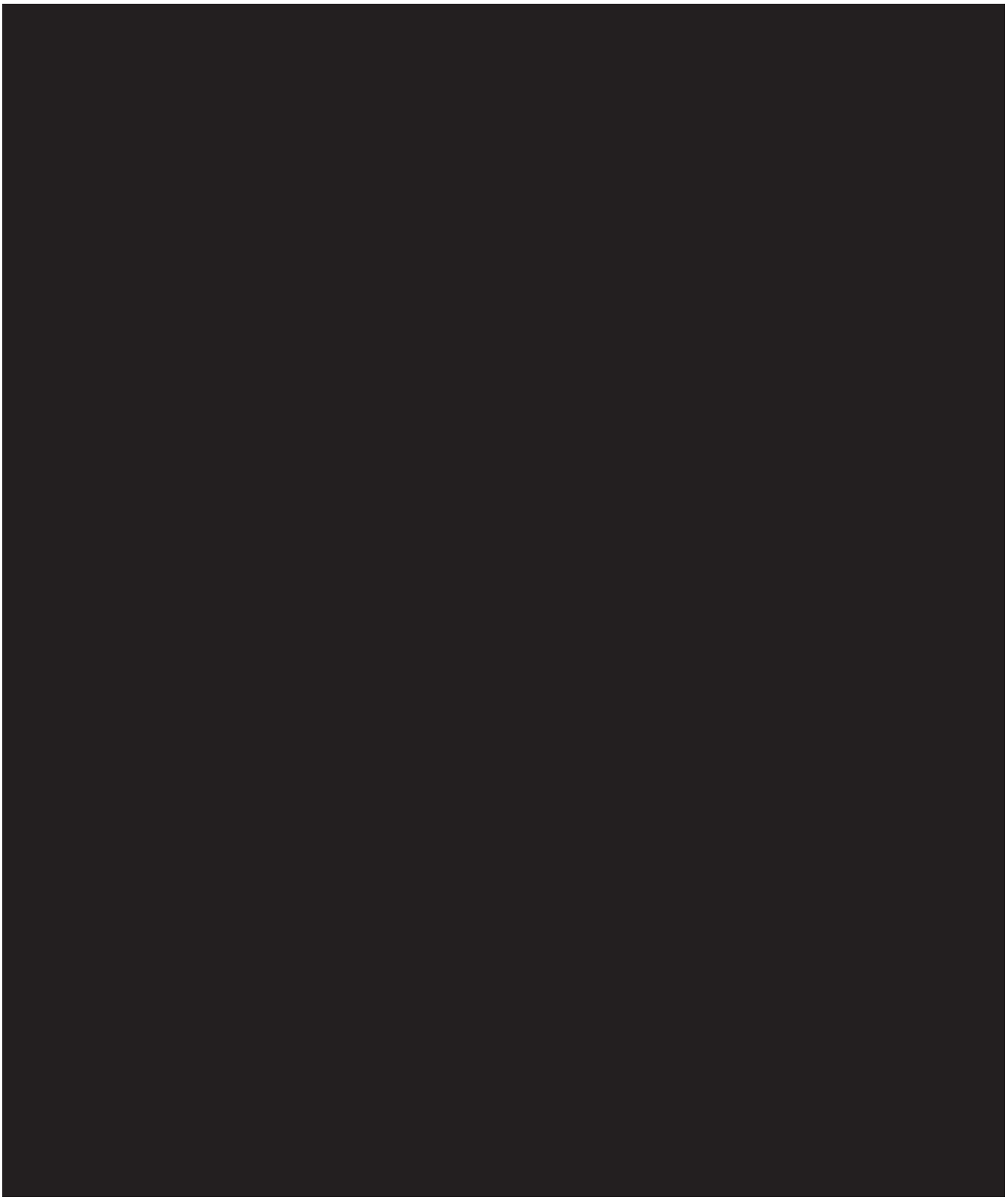
Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives); of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)
- Disappearance of the event even though the trial drug treatment continues or remains unchanged



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[redacted]

5.6 OTHER ASSESSMENTS

5.6.1 Eligibility assessment

Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short structured clinical interview which enables researchers to make diagnoses of psychiatric disorders (R07-1303). It should be performed at screening (Visit 1) for eligibility confirmation.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are acceptable measurements in monitoring safety aspects or assessing treatment response in patients with CIAS. In particular, the scheduled safety assessments are appropriate to see drug-induced changes in physical examination, vital signs, ECG and standard laboratory values.

[redacted]

A Phase II study of encenicline (a selective α7 nicotinic acetylcholine receptor agonist) as a treatment for CIAS demonstrated clinically meaningful improvements in cognition and function in patients with Schizophrenia over 12 weeks (R16-2465). Thus, the treatment period of 12 weeks with BI 425809 is considered to be appropriate to see a change in cognitive function in schizophrenic patients.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart including time windows 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 2). The trial medication kits 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 AE 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.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

The following guidance pertains to conduct of the neuropsychological assessments:

- Each assessment of the rating scales (MCCB, SCoRS, PANSS, [redacted]) should preferentially be done by the same members of the site staff for a given patient throughout the study period
    - Note: 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 assessments at Visit 4 and (e)EoT Visit must be started at the same time of the day as at Visit 2 (+/- 60 minutes)**; in case this cannot be done at a scheduled visit, then the visit should be rescheduled within the allowed visit window
- The MCCB assessment should preferably be done in the morning
- The screening MCCB assessment must be done before start of CCT run-in and at least 12 days prior to the baseline MCCB assessment at Visit 2
- Visit 2 should be done within 7 days after patient completes the CCT run-in whenever possible
    - During the screening period, once eligibility based on CCT run-in is established, the patient should not complete any further CCT until they are randomized to the treatment period.
- The neuropsychological assessments should be conducted in the following order:
    - Screening (Visit 1) and Visit 4: The MCCB is done first before other neuropsychological assessments
    - Visit 2 and (e)EoT Visit: The [redacted] MCCB is done [redacted] before other neuropsychological assessments

- Study procedures for Visit 2 and (e)EoT Visit can be split into 2 sequential days (i.e. 2 consecutive calendar days), in which case: the [redacted], MCCB [redacted] should be performed on the first day (for Visit 2, this should preferably be done within 7 days after patient completes the CCT run-in); the other neuropsychological assessments (i.e. PANSS, SCoRS, [redacted]) should be performed on the second day (for Visit 2, this would be day of first study drug intake).
- During the neuropsychological testing, patients are allowed to take short breaks as needed, in the judgement of the rater/investigator
- The site staff must be properly trained on all trial procedures 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
    - In addition, the site staff that will be administering the neuropsychological performance and clinical rating scales may require certification

The following information applies to the CCT and related activities:

- The CCT exercises will come from the CR-Psychiatry program provided via the [redacted]
- Patients will use a personal computer (laptop/desktop) or tablet device with web browser to access the CCT exercises through the internet; each patient will need to log into their own account within the [redacted] in order to access and complete their CCT exercises
- All CCT training data is saved on a secure server by the CCT vendor; data can then be viewed by sponsor and site staff through a secure, password-protected and HIPAA-compliant clinician server (CCT "portal")
    - Note: These data will only be used to ensure compliance with the use of CCT; they will not be used to display or analyze medical information about a patient, they will not be used to support or provide recommendations about prevention, diagnosis or treatment, and they will not be used to enable review the basis for such recommendations with the intent of making treatment decisions
- Each participating site will identify a CCT "coach" who will supervise use of the CCT program by study participants; the CCT coach performs various functions including:
    - Creates patient accounts within the [redacted]
    - Manages allocation and return of CCT devices
    - Provides training/re-training as necessary on the proper use of the CCT program
    - Proactively contacts patients at least weekly during the treatment period (more frequent contacts may be warranted during the CCT run-in) to provide guidance and encouragement to complete assigned CCT exercises, and to ensure that the CCT program is problem-free
    - Monitors CCT compliance remotely via CCT portal on an ongoing basis (at least weekly although more frequent checks are encouraged during the CCT

run-in) and follows up with patients as necessary to discuss compliance status and encourage them to complete CCT to target (i.e. 2.5 hours per week divided into 3-5 sessions of 30-50 minutes duration)
    - Is available to remotely assist study patients in case of technical difficulties or questions regarding the CCT program
- All sites will receive a CCT Manual (available in the ISF) containing further details regarding the CCT program and CCT coach role and responsibilities
- Patients should try to avoid antihistaminic, benzodiazepine or other sedative medication within 8 hours before CCT training sessions, if possible

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

During the COVID-19 pandemic, there might be situations when patients already in the study might not be able to come to the site for the scheduled visit. This might be due to restrictions set by authorities or by the investigator site/institution, because the patient is quarantined, or because of any patient specific situation that the investigator judges as being not safe for the patient to come to the site.

For details on potential modifications of the trial conduct related to the COVID-19 pandemic, please refer to Section 10.5.

6.2.1 Screening and run-in period(s)

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

All procedures for screening (Visit 1) as listed in the Flow Chart have to be performed within 28 days (or within 38 days if cannabis re-testing is performed) prior to Visit 2 (date of first drug administration) and can occur on more than one day. It is recommended that Visit 1 laboratory samples are collected as early as possible in the screening period.

Baseline conditions and medical history will be recorded, including but not limited to:
- Demographics such as gender, age, ethnicity, smoking and alcohol history
- All concomitant medications.
- Psychiatric and relevant non-psychiatric history
    - Baseline disease state will be assessed by PANSS

The following assessments will be completed to assess eligibility:
- PANSS Positive scale item P1-P7 will be used for confirming eligibility at Visit 1 and Visit 2
- The M.I.N.I. and the ‘Baseline / Screening’ version of the C-SSRS will be administered for eligibility confirmation

The SCoRS assessment will be done during screening (Visit 1).

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.

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 women of childbearing potential must perform urine (dipstick) pregnancy test at screening (Visit 1). The urine dipstick test will be completed locally on-site using kits provided by central lab. In the event of a positive urine pregnancy test, a serum pregnancy test will be performed by the central lab for confirmation.

During screening, the investigator should highlight to patients the importance of not taking drugs of abuse during the study, and that the urine drug screen will be repeated periodically throughout the trial. Patients should also be informed that they cannot participate in the trial if they have a positive urine drug screen (see further the relevant exclusion criterion in Section 3.3.3).

The screening MCCB assessment must be done before start of CCT run-in and it is recommended that as many of the other screening procedures as possible also should be assessed prior to start of CCT run-in. The process for completion of CCT run-in includes the following:

- Preferably within 7 days after written informed consent signed (enrolment), patients that still meet eligibility criteria (according to available information) will begin the CCT run-in; this will be considered day 1 of the CCT run-in
- On day 1 of the CCT run-in, the following will be completed by the CCT coach:
    - Provide initial training to patient on use of the CCT program; patients with little or no experience using a personal computer (laptop/desktop) or tablet device may require additional training from the CCT coach on how to properly use the CCT device
    - Supervise the first CCT session at the clinic to ensure the patient is able to demonstrate proper use of the CCT device and program
    - Allocate a CCT device to the patient, if needed (i.e. if patient does not have or is not willing to use their own device or does not have reliable internet access)
- During the CCT run-in (2 weeks), the CCT coach will:
    - Proactively contact patient at least weekly (although more frequent contacts may be warranted) to provide guidance and coaching about their progress, and ensure that the CCT program is problem-free
    - Monitor CCT compliance remotely via CCT portal on an ongoing basis (at least weekly although more frequent checks are recommended) and follow up with patients as necessary to discuss compliance status and encourage them to complete CCT exercises to target

- Following completion of the CCT run-in, the CCT coach will review compliance against the related eligibility criterion

Refer to the CCT Manual for further details regarding completion of CCT during run-in.

Once Visit 1 procedures (including CCT run-in) are complete including laboratory results are received, all data collected should be reviewed against the inclusion/exclusion criteria.

If the patient is still eligible, the patient should be contacted to schedule next visit (Visit 2).

If the patient is not still eligible (i.e. if they are considered a screen failure), they should be contacted to arrange return of the CCT device. The patient must be recorded as a screen failure in eCRF and registered as screen failure in IRT.

Patients who fail screening, including low compliance with the CCT run-in, may repeat the screening period once after discussion between investigator and sponsor. Re-screening will only be allowed if there is a reasonable explanation, and the reason would not jeopardize compliance throughout the trial based on investigator judgement. Permission to re-screen patients must be obtained from the CTM or CTL. Re-screening must be registered in the IRT. Patients who are re-screened need to be re-consented and given a new patient number. All the study procedures for screening (Visit 1) must be repeated with the exception of CCT run-in if related compliance was confirmed before the patient failed screening initially.

6.2.2 Treatment period(s)

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

Throughout the treatment period, vital signs and ECG should always be measured before any blood samples are taken.

At Visit 2 and as needed throughout the treatment period based on investigator judgement, patients should be reminded about the importance of not taking drugs of abuse during the study, and that the urine drug screen will be repeated periodically throughout the trial. Patients should also be reminded to avoid taking antihistaminic, benzodiazepine or other sedative medication within 8 hours of MCCB visits, if applicable.

[redacted]

The process for completion of CCT during the treatment period includes the following:

- For randomized patients, the same CCT device and related equipment as used for CCT run-in will continue to be used during the treatment period
- All CCT exercises during the treatment period will be completed by patients independently, most likely at home, without clinician intervention
- During the treatment period, the CCT coach will:

- Proactively contact patient at least weekly (between scheduled clinic visits), according to their preferred method of contact, to provide guidance and coaching about their progress, and ensure that the CCT program is problem-free
- Monitor CCT compliance remotely via CCT portal on an ongoing basis (at least weekly) and follow up with patients as necessary to discuss compliance status and encourage them to complete CCT exercises to target

Refer to the CCT Manual for further details regarding completion of CCT during the treatment period.

Randomization (Visit 2)

At the start of Visit 2 it should be ensured that all Visit 1 procedures have been successfully completed and eligibility has been confirmed.

This visit includes the assessment of the endpoints (baseline) and randomization via IRT.

The baseline MCCB assessment at Visit 2 should preferably be done within 7 days after patient completes the CCT run-in.

At Visit 2, patients eligible for randomization will meet with the CCT coach to review their experience during the CCT run-in, receive re-training on use of the CCT program (if necessary) and further instructions for continuing CCT during the treatment period.

IRT should not be called in the event of a positive urine pregnancy test (to be completed locally on-site using kits provided by central lab). In this case, a serum pregnancy test will be performed by the central lab for confirmation, and a negative serum pregnancy test result must be received before the patient can be randomized.

Upon randomization via the IRT, sufficient trial drug for 28 days (21 treatment days plus 7 days reserve) will be dispensed. The first dose should be taken at the clinic after all Visit 2 assessments are completed.

Visit 3, Visit 4 and Visit 5

Patients should not take trial medication before coming to the clinic at Visit 3, Visit 4 and Visit 5. This is because patients will be dosed at the clinic after safety lab samples [redacted] are taken. [redacted]

Patients should be instructed to bring all trial medication (used and unused kits/packaging including blisters) with them to these clinic visits.

Sufficient trial drug for 28 days (21 treatment days plus 7 days reserve), as assigned by IRT, will be dispensed at each visit.

In the event of a positive urine pregnancy test (and positive confirmatory serum pregnancy test), the study medication will be stopped, the patient will be discontinued from the trial and will be followed up until birth or otherwise termination of the pregnancy. See further Section 3.3.4.1 and Section 5.2.6.2.

At each of these visits, the CCT coach should meet with patients to discuss their experience and progress with the CCT exercises, and to provide re-training on CCT as needed.

At Visit 5, patients will be instructed to take the last dose of study medication on the **day before** the EoT Visit. In case the EoT Visit is split into 2 sequential days (i.e. 2 consecutive calendar days), the last dose of study medication should be taken on the day before the first day of the split visit.

Visit 6/End of Treatment (EoT) Visit/early End of Treatment (eEoT) Visit

[redacted]

Also for patients that complete the treatment period, the final MCCB assessment at the EoT Visit must be performed **after** patient completes the full 12-week (84 days) treatment period. The EoT Visit cannot be done before Day 84 (see further the visit window for the EoT Visit as described in the Flow Chart).

For patients who discontinue study medication early, the MCCB assessment for the eEoT Visit must be performed within 7 days after last dose intake.

If the patient was allocated a CCT device, this will be collected at the (e)EoT Visit.

In the event of a positive urine pregnancy test (and positive confirmatory serum pregnancy test) at the (e)EoT Visit, the patient will be followed up until birth or otherwise termination of the pregnancy. See further Section 3.3.4.1 and Section 5.2.6.2.

6.2.3 Follow-up period and trial completion

For patients that complete the treatment period, a Follow up Visit will be conducted 28 days after the EoT visit based on the half-life of the trial medication.

If patient discontinues the trial early, the Termination of Trial Medication eCRF page must be completed and a Follow-up Visit should be completed 28 days after eEoT Visit.

AEs which have not recovered at Follow-up Visit should be followed up until they are resolved, have been assessed as “chronic” or “stable”, or no further information can be obtained.

All patients with Hb drop below 100 g/L (10 g/dL) or absolute decrease >20 g/L (2 g/dL) since baseline (Visit 2) will need to be followed up post-end of study until value returns to baseline/normal value, or resolution (per investigator's judgment).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomized, double-blind, placebo-controlled, parallel group trial with a 12-week Treatment Period. The primary objective of this trial is to provide PoC data by assessing the effect on cognition of oral once daily administration of BI 425809 given for 12 weeks in patients with schizophrenia on stable antipsychotic treatment and adjunctive CCT.

The primary endpoint is change from baseline in neurocognitive function as measured by the neurocognitive composite score of the MCCB after 12 weeks of treatment, which is the overall MCCB composite score excluding the Social Cognition domain score. A detailed description of the model utilized is provided in Section 7.3.1.

For a description of the secondary endpoints, please refer to Section 2.1.3.

7.2 NULL AND ALTERNATIVE HYPOTHESES

This trial is designed to assess the effects of BI 425809 with adjunctive CCT and placebo with adjunctive CCT on cognition in patients with schizophrenia on stable antipsychotic treatment.

There will be no formal hypothesis testing performed. Inference concerning the efficacy of BI425809 with adjunctive CCT will be accessed based on the estimated mean difference(s) between the treatment and placebo arm on the MCCB neurocognitive composite score change from baseline after 12 weeks of treatment, as well as other efficacy endpoints.

7.3 PLANNED ANALYSES

The following patient analysis sets are defined for this trial:

- Randomized Set (RS): includes all patients who signed informed consent and were randomized to receive either BI 425809 + CCT or placebo + CCT.
- Treated Set (TS): includes all patients in RS who were treated with at least one dose of the trial regimen (including both drug and CCT). Patients in TS are analyzed under the actual trial regimen received at randomization. The TS is used for safety analyses as well as demographics and baseline characteristics and treatment regimen exposure.
- Full Analysis Set (FAS): includes all patients in treated set who had non-missing baseline and at least one non-missing post-baseline on-treatment measurement on the primary efficacy endpoint. The FAS is used for efficacy analyses and patients will be analyzed as randomized.
- [redacted]

Data from patients who were screened but not randomised will be listed but not included in any inferential statistics.

[redacted]

The list of IPDs is described in the study TSAP.

Handling of randomised patients who received the wrong treatment will be specified in the TSAP.

Baseline

The baseline for MCCB neurocognitive composite score, and all other efficacy-related endpoints is defined as the measurement taken at randomization (Visit 2), and prior to the first administration of the study drug.

7.3.1 Primary endpoint analyses

The primary analysis of the primary efficacy endpoint will be performed on FAS. The Restricted Maximum Likelihood (REML)-based MMRM model will be fitted for the change from baseline in the MCCB neurocognitive composite score after 12 weeks of treatment. The model will include the continuous baseline MCCB neurocognitive composite score, and change in the MCCB neurocognitive composite score from screening to baseline as covariates, treatment (BI 425809 + CCT vs. placebo + CCT), age (<=40 vs. >40) and visit as factors, as well as the treatment-by-visit and baseline-by-visit interactions. Patient will be treated as random effect. The unstructured variance-covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Analyses will be implemented using SAS PROC MIXED. The primary treatment comparisons will be the contrasts between treatment groups (BI 425809 + CCT vs. placebo drug + CCT) at Week 12. Estimated least squares mean difference between treatment arms will be provided.

[redacted]

For the definition of MCCB neurocognitive composite score, please refer to Section 7.1.

7.3.2 Secondary endpoint analyses

A specification of secondary endpoints is provided in Section 2.1.3.

The analyses of efficacy-related secondary endpoints will be performed in FAS. The same model utilized for the primary endpoint will be fitted for change from baseline in the overall MCCB composite score. For change from baseline in PANSS total score after 12 weeks of treatment, an MMRM model that includes treatment, age and visit as factors, the corresponding baseline value as a covariate, as well as treatment-by-visit and baseline-by-visit interactions will be fitted. For change from baseline in SCoRS score after 12 weeks of treatment, an ANCOVA model that includes treatment and age as factors, and its corresponding score at baseline as a covariate will be fitted. The adjusted mean values as well as the treatment group contrasts at week 12 will be presented together with the 95% confidence intervals (CI). All p-values will be considered descriptive.

For the percentage of patients with (S)AEs (including clinically relevant abnormalities of physical examination, vital signs, ECG and laboratory tests), comparison will be made for (BI 424809 + CCT) group vs. (placebo + CCT) group on TS together with descriptive statistics.

For other secondary endpoints, only descriptive statistics and exploratory analyses will be provided.

Other analyses may be considered if deemed necessary and the details will be provided in the TSAP.

[redacted]

7.3.4 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment and the end of the REP, a period of 11 days after the last dose of trial medication, will be assigned to the on Treatment Period for evaluation.

All treated patients will be included in the safety analysis. 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 AEs will concentrate on treatment-emergent adverse events, i.e. all AEs occurring between start of treatment and end of the REP. AEs that start

before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at the database lock.

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 summarised. 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 (Visit 1), baseline (Visit 2), 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.

[redacted]

[redacted]

7.5 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at the pre-planned time points. Handling of missing data in MCCB tests will follow the MCCB Manual (available in the ISF). In general, for completely missing visit missing data will not be imputed and will be handled through the MMRM under the "missing at random" assumption. BI standards will be used for missing data in AE, safety lab, [redacted]. The missing data handling rules will be further specified in details in the TSAP.

7.6 RANDOMIZATION

Eligible patients will be stratified by age (age 18-40 and age 41-50) and will be randomized with 1:1 ratio to the BI 425809 10 mg + CCT and placebo + CCT arms. The randomization will be implemented in blocks to achieve balanced allocation to each of the two treatment arms. The block size will be documented in the clinical trial report (CTR).

The randomization will be conducted via an IRT. BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated by a validated system, which utilizes a pseudo-random number generator to make the resulting treatment sequence both reproducible and non-predictable. Access to the randomization codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to randomize a total of 200 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial.

Based on this sample size, the probabilities for observing a mean difference < 0.3, 0.3 - 0.4, or > 0.4 between the treatment arm and the placebo arm on the change from baseline MCCB neurocognitive composite score after 12 weeks of treatment are displayed in Table 7.7: 1.

For these calculations, the following assumptions are made. A total of 200 patients are randomized. Assuming a10% dropout rate this leads to a total of 180 evaluable subjects.

Table 7.7: 1 Probabilities of observing a mean difference in the primary endpoint < 0.3, 0.3 – 0.4, or > 0.4 for treatment relative to placebo arm under different scenarios (90 evaluable patients per arm).

True effect size relative to placebo	Probability to observe a mean difference of (BI 425809 vs. Placebo)		
BI 425809	< 0.3	0.3 – 0.4	> 0.4.
0.5	0.092	0.159	0.749
0.45	0.158	0.204	0.638
0.4	0.251	0.242	0.507
0.35	0.362	0.270	0.368
0.3	0.493	0.255	0.252
0.25	0.632	0.211	0.157
0.2	0.748	0.163	0.089

The calculation was performed using R version 3.3.2, based on 10000 simulations.

Hence, assuming the true effect size is 0.45, there is a 64% probability to observe a mean difference between the treatment and placebo arms greater than 0.4, and an 84% probability to observe a mean difference of at least 0.3. On the other hand, assuming the true effect size is only 0.2, there is a 75% probability of observing a mean difference less than 0.3, and a 91% probability of observing a mean difference of at most 0.4.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

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-GCP, relevant BI Standard Operating Procedures (SOPs), and other current relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains 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 patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH-GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the CTR.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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.

8.2 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / 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.

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

If study conduct may need to be adjusted during the COVID-19 pandemic (see Section 6.2 and Section 10.5), the patient must be made aware of any modifications and provide their agreement to the modifications prior to them being implemented.

The consent and re-consenting process should be properly documented in the source documentation.

8.3 RECORDS

CRFs 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

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).
Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. If medical records cannot be obtained prior to randomization, a phone call with the treating physician(s) detailing eligibility information must be conducted and documented, and the documentation filed with the subject's source records. If medical records cannot be obtained and a phone call with the treating physician(s) cannot be conducted, the CTM or CTL should be contacted for further discussion.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. United States Food and Drug Administration). They may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH-GCP.

8.3.3 Storage period of records

Trial site(s)

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the World Health Organization Good Clinical Practices handbook and the EU General Data Protection Regulation.

Personalised 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 at the site 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.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Not applicable

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

The "**Last Patient Last Treatment**" (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / CA in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to the BI clinical trial portal Clinergize to access documents provided by the sponsor.

BI has appointed a CTL, responsible for coordinating all required activities, in order to
- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of CTMs, CRAs, and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.
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 are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service, a central images service for ECG, an IRT vendor and a vendor for delivery of the CCT exercises will be used in this trial. Details will be provided in the Central Laboratory Manual, ECG Manual, IRT Manual and CCT Manual, respectively, available in the ISF.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

Further instructions for use of the CCT program will be described in the CCT Manual available in the ISF.

Additionally, instructions for use of the central laboratory service, central images service for ECG and IRT system will be described in the Central Laboratory Manual, ECG Manual and IRT Manual, respectively, available in the ISF.

[redacted]

10.5 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19

As mentioned in Section 6.2, in case of any new restrictions during the COVID-19 pandemic and for patients already in the study, study conduct may need to be adjusted based on the investigator's discretion (and agreed with the sponsor). The following contingency measures have been introduced to ensure patient safety and appropriate trial continuation based on a thorough benefit-risk assessment of treatment continuation versus early discontinuation, to be judged by the investigator on an individual patient level whereby patient safety always needs to be at the centre of decision-making (see Section 1.4).

In exceptional cases, when it is impossible to conduct the visits at the trial site, visits may be performed at the patient's home or remotely (via telephone and/or internet based means of communication). The visits may also be performed as a combination of home and remote visits. Based on a thorough benefit-risk assessment (see Section 1.4), the visit procedures may be adjusted for the purpose of particular visits, whereby critical safety measures will remain in place. All home/remote visits need to be discussed with and approved by the sponsor.

Local regulatory and legal requirements of the participating country need to be respected for all modifications. Patients need to be informed about the modifications and agree to them before implementation (see Section 8.2).

Under these circumstances, the below modifications can be considered.

Remote visit

If a patient is not able to come to the site for an in-clinic trial visit, a remote visit (by phone) should be performed instead and all assessments that can be done by phone performed.

The following study data may be collected/reported during phone contacts: Adverse events, concomitant therapies, C-SSRS, birth control check (for women of childbearing potential), SCoRS and PANSS, [redacted], and study medication and CCT compliance checks. Patients can report and/or send photos of study medication kit used to their site staff, if needed and possible.

Additional guidance for assessing specific symptoms as part of adverse event check during phone contacts is available to investigators and should be followed.

MCCB cannot be done via phone, but in certain situations it may be possible to complete some MCCB sub-tests (enough to derive a composite score) via videoconference between the rater and the patient, if agreed with sponsor. If necessary during COVID-19 pandemic, based on the REP for BI 425809 (as defined in Section 1.2), Visit 6/(e)EoT Visit may be delayed up to 10 days following the last dose of trial medication, in case this helps to facilitate an in-clinic trial visit with MCCB assessment.

Safety and other laboratory tests, vital signs, ECG

If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local laboratory. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF. Recommended minimum safety lab parameters are: Hematology, Urea (BUN), Creatinine, eGFR, liver enzymes, pregnancy test (for WOCBP).

If home visits are possible, some assessments can be done at the patient's home (e.g. collection of blood and urine samples to be sent to the central lab, vital signs).

Direct-to-patient shipment of trial medication

If a patient is not able to come to Visit 3, Visit 4 or Visit 5 as planned but the investigator considers it favorable and safe for the patient to continue on trial medication, the trial medication can be shipped from site directly to the patient (if acceptable according to local laws and regulations). Such shipments require the use of a sponsor approved courier to the patient's home. Investigators should conduct phone visits first to discuss adverse events, concomitant therapies, C-SSRS, birth control check, and assess study medication and CCT compliance. If possible and as per investigator's clinical judgement, safety laboratory tests should be done at a local laboratory.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		21 DECEMBER 2018
EudraCT number **EU number**		2018-002740-82
BI Trial number		1346-0038
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 BI 425809 once daily with adjunctive Computerized Cognitive Training over 12 week treatment period in patients with schizophrenia
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
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		Lay Title
Description of change		"combined with" changed to "together with"
Rationale for change		To simplify language and better describe intended use of Computerized Cognitive Training for this study
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		"proof of clinical concept (PoCC)" changed to "proof of concept (PoC)"
Rationale for change		To reflect exploratory nature of the study
Section to be changed		Flow Chart
Description of change		"Days" from first randomized treatment amended for visits during the treatment period
Rationale for change		Visit 2 (randomization) is more accurately zero (0) days from first randomized treatment, rather than 1 day from first randomized treatment; number of days from first randomized treatment was revised accordingly for Visit 3, Visit 4, Visit 5 and Visit 6/EoT
Section to be changed		Flow Chart
Description of change		Addition to footnote 9 describing audio recording of patient and study partner interviews for SCoRS and PANSS assessments
Rationale for change		To explain that interviews will be audio recorded

		for Quality Control purposes
Section to be changed		ABBREVIATIONS
Description of change		Proof of Clinical Concept (PoCC) changed to Proof of Concept (PoC)
Rationale for change		PoCC will no longer be referenced in the protocol, replaced with PoC
Section to be changed		1.1
Description of change		Revised background information on cognitive training
Rationale for change		To highlight that cognitive training will be used in this study only as background cognitive stimulation
Section to be changed		1.3
Description of change		Revised points regarding cognitive training
Rationale for change		To highlight that cognitive training will be used in this study only as background cognitive stimulation
Section to be changed		1.4
Description of change		PoCC changed to PoC
Rationale for change		Clarification
Section to be changed		1.4
Description of change		Revised description of cognitive training
Rationale for change		To highlight that cognitive training will be used in this study only as background cognitive stimulation
Section to be changed		2.1.1
Description of change		PoCC changed to PoC and explanatory text added
Rationale for change		To reflect the exploratory nature of the study
Section to be changed		3.3.3
Description of change		Exclusion criterion no. 24 was amended to remove exception for Benzodiazepines
Rationale for change		Benzodiazepines are not included in the urine drug screen
Section to be changed		3.3.3
Description of change		New exclusion criterion no. 28 added to exclude patients with an allergy to BI 425809 and/or any of the excipients (including lactose) or placebo ingredients
Rationale for change		Additional safety consideration
Section to be changed		4.2.1
Description of change		Revised wording regarding decision for CCT schedule
Rationale for change		To better explain choice of CCT schedule for the study
Section to be changed		4.3
Description of change		Removed wording regarding the planned automated notifications and reminders
Rationale for change		Automated notifications and reminders will not be used

Section to be changed		7.1
Description of change		PoCC changed to PoC
Rationale for change		Clarification
Section to be changed		8
Description of change		Removal of reference to medical device regulations
Rationale for change		Previous text does not apply to this study

11.2 GLOBAL AMENDMENT 2

Date of amendment		02 OCTOBER 2019
EudraCT number **EU number**		2018-002740-82
BI Trial number		1346-0038
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 BI 425809 once daily with adjunctive Computerized Cognitive Training over 12 week treatment period in patients with schizophrenia
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Revision to Statistical Methods section to indicate change from screening to baseline MCCB neurocognitive composite score, rather than baseline to screening
Rationale for change		To correct typo
Section to be changed		Flow Chart
Description of change		CCT compliance check and CCT progress reviewed and re-training/reminders to patients as needed added during Screening Period
Rationale for change		To align with Section 6.2
Section to be changed		Flow Chart, footnote (*)
Description of change		Recommendation for screening laboratory samples be collected as soon as possible following enrolment
Rationale for change		To encourage assessment of laboratory results prior to start of CCT run-in
Section to be changed		Flow Chart, footnote (*)
Description of change		Allowance for an extension of the Screening Period of up to 10 days (for total 38 days) in case cannabis re-testing per exclusion criterion 24 is performed

Rationale for change		Logistical, to allow for some time to pass (per investigator discretion) between initial urine drug screen and cannabis re-test
Section to be changed		Flow Chart, footnotes [1] and [12]
Description of change		Addition of word "preferably" to describe timing of procedures in relation to CCT run-in
Rationale for change		To clarify that defined overall screening window from Visit 1 to first drug administration should be the priority consideration
Section to be changed		Flow Chart, footnote [3]
Description of change		Clarification that a serum pregnancy test will be performed by central lab if urine test positive, independent of Investigator discretion
Rationale for change		To align with central laboratory manual
Section to be changed		Flow Chart, footnote [12]
Description of change		Clarify that once CCT run-in compliance is established, no further CCT should be completed until patient is randomized, and that CCT run-in should not be repeated for re-screened patients if already confirmed before screening failure
Rationale for change		To minimize CCT exposure prior to randomization
Section to be changed		3.3.3
Description of change		Addition to Exclusion criterion 19 to exclude patients with known history of HIV infection "based on review of medical history"
Rationale for change		Clarification that active HIV testing at Visit 1 is not intended
Section to be changed		3.3.3
Description of change		Revision of Exclusion criterion 24 to remove timeframe for cannabis re-testing
Rationale for change		Timeframe for re-testing should be at the investigator's discretion and based on when the patient last used cannabis
Section to be changed		4.2.1
Description of change		Removal of statement that CCT sessions must be minimum 10 consecutive minutes to be included in weekly accrual time
Rationale for change		[redacted] CCT program does not identify short training segments for site users
Section to be changed		4.3
Description of change		Add that site should discuss with patient to determine reason if the number of doses taken is greater than 100%
Rationale for change		Comment required in eCRF if the number of doses taken is greater than 100%, per FDA request for all CNS active medication

Section to be changed		4.3
Description of change		Replacement of statement that CCT sessions must be minimum 10 consecutive minutes to be included in weekly accrual time with preference for training to be done for a minimum of 10 minutes
Rationale for change		[redacted] CCT program does not identify short training segments for users
Section to be changed		4.3
Description of change		Addition of word “preferably” to describe timing of procedures in relation to CCT run-in
Rationale for change		To clarify that defined overall screening window from Visit 1 to first drug administration should be the priority consideration
Section to be changed		4.3 and 6.2
Description of change		Clarify that once CCT run-in compliance is established, no further CCT should be completed until patient is randomized
Rationale for change		To minimize CCT exposure prior to randomization
Section to be changed		4.3
Description of change		Revision of description of protocol deviation for CCT non-compliance
Rationale for change		Clarification
Section to be changed		5.2.6.2
Description of change		To provide clarification regarding the process for AE collection
Rationale for change		Clarification
Section to be changed		6.2
Description of change		The MCCB assessments at Visit 4 and (e)EoT Visit must be started at the same time of the day as at Visit 2 (+/- 60 minutes)
Rationale for change		The Visit 2 MCCB assessment (not the Visit 1 MCCB assessment) should be considered as baseline for start time of subsequent MCCB assessments
Section to be changed		6.2, 6.2.1, 6.2.2
Description of change		Addition of word “preferably” to describe timing of procedures in relation to CCT run-in
Rationale for change		To clarify that defined overall screening window from Visit 1 to first drug administration is the priority consideration
Section to be changed		6.2.1
Description of change		Addition of recommendation to collect Visit 1 laboratory samples as early as possible in the screening period
Rationale for change		To encourage assessment of laboratory results prior to start of CCT run-in

Section to be changed		6.2, 6.2.1 and 6.2.2
Description of change		Deletion of statements indicating provision of related CCT device equipment
Rationale for change		No related equipment to be provided
Section to be changed		6.2 and 6.2.1
Description of change		Addition of encouragement for more frequent checks of CCT compliance during run-in
Rationale for change		To allow more timely patient follow-up if compliance not meeting eligibility requirements
Section to be changed		6.2.1 and 6.2.2
Description of change		Clarification at all relevant visits that a serum pregnancy test will be performed by central lab if urine test positive, independent of Investigator discretion
Rationale for change		To align with central laboratory manual
Section to be changed		6.2.1
Description of change		Addition of reason for CCT device allocation
Rationale for change		To avoid CCT compliance issues due to patient's lack of internet availability
Section to be changed		6.2.1
Description of change		Clarify that CCT run-in should not be repeated for re-screened patients if already confirmed before screening failure
Rationale for change		To minimize CCT exposure prior to randomization
Section to be changed		6.2.2
Description of change		Clarification that EoT visit cannot be done before Day 84, rather than Day 85
Rationale for change		To align with changes to Flow Chart in Global Amendment 1
Section to be changed		6.2.2
Description of change		Deletion of instructions at EoT relating to procedures in the event of positive pregnancy test
Rationale for change		To correct error
Section to be changed		7
Description of change		Slight changes to wording (grammatical)
Rationale for change		For clarity and to correct typo
Section to be changed		7.3.1
Description of change		Revision to indicate change from screening to baseline MCCB neurocognitive composite score, rather than baseline to screening
Rationale for change		To correct typo
Section to be changed		8
Description of change		Addition of statement that the trial will be carried out in accordance with the Medical Devices Directive and the harmonised standards for Medical Devices

Rationale for change		Sponsor to provide ECGs as loaned equipment, which would be considered a medical device
Section to be changed		8.1
Description of change		Deletion of reference to Clinergize as an electronic ISF
Rationale for change		To reflect the requirement for all original records generated at a site to be retained within the local ISF on-site
Section to be changed		10.4
Description of change		Revision of Day numbers in Table 10.4.1: 1
Rationale for change		To align with changes to Flow Chart in Global Amendment 1
Section to be changed		11.1
Description of change		For previous Global Amendment 1, "X" placed in tick box associated with implementation instruction "To be implemented only after approval of the IRB / IEC / Competent Authorities"
Rationale for change		Tick box previously not filled

11.3 GLOBAL AMENDMENT 3

Date of amendment		21 Jul 2020
EudraCT number **EU number**		2018-002740-82
BI Trial number		1346-0038
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 BI 425809 once daily with adjunctive Computerized Cognitive Training over 12 week treatment period in patients with schizophrenia
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS Main in- and exclusion criteria
Description of change		Remove reference to psychotropic medications in general with examples
Rationale for change		Alignment with change to section 3.3.2 inclusion criterion 4
Section to be changed		FLOW CHART
Description of change		For the Trial Period corresponding to the Follow-up Visit, change name from "End of Trial" to "End of Study"

Rationale for change		Avoid any confusion with the End of Trial (EoT) Visit
Section to be changed		FLOW CHART
Description of change		Add SCoRS assessment to Visit 1 (Screening)
Rationale for change		Pre-exposure to SCoRS at Visit 1 will allow Study Partners to anticipate the questions that will be asked at the baseline SCoRS assessment at Visit 2 and observe the patient more closely leading up to the baseline assessment, thereby allowing for enhanced quality of the Study Partner contribution to the baseline SCoRS assessment
Section to be changed		FLOW CHART footnote (*****)
Description of change		Instruction that, following patient's trial participation, only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of should be reported and only via the BI SAE form, in alignment with wording in Section.5.2.6.2
Rationale for change		Additional reminder to investigator
Section to be changed		FLOW CHART footnotes 1, 5 and 6
Description of change		Added clarification that split visits are to be done on 2 consecutive calendar days
Rationale for change		Avoid the possible misinterpretation of the word "sequential" that could lead to a split visit being done a Friday and the following Monday
Section to be changed		FLOW CHART footnote 13
Description of change		Additional note that any hemoglobin decrease >20 g/L (2 g/dL) since baseline (Visit 2) or leading to symptoms of anemia (e.g. dyspnea, dizziness, etc) will require safety follow-up with safety lab at the next visit(s), or earlier if considered necessary by the investigator
Rationale for change		Reminder for investigators, in alignment with new text in Section 5.2.6.2
Section to be changed		FLOW CHART footnote 14
Description of change		Additional note that all patients with hemoglobin drop below 100 g/L (10 g/dL) or absolute decrease >20 g/L (2 g/dL) since baseline (Visit 2) will need to be followed up post-end of study until value returns to baseline/normal value, or resolution (per investigator's judgment)
Rationale for change		Reminder for investigators, in alignment with new text in Section 6.2.3
Section to be changed		1.2
Description of change		Various changes to Drug Profile wording based on updated IB

Rationale for change		Alignment with updated Investigator's Brochure
Section to be changed		1.4
Description of change		Various changes to Benefit-Risk Assessment wording based on updated IB
Rationale for change		Alignment with updated Investigator's Brochure
Section to be changed		3.3
Description of change		Updated planned number of trial centres and countries participating in the trial, indicated as range
Rationale for change		To reflect current planned number of trial centres and countries participating in the trial
Section to be changed		3.3.2 inclusion criterion 4
Description of change		Remove reference to psychotripic medications in general with examples
Rationale for change		Greater clarity regarding the medications that pertain to this inclusion criterion
Section to be changed		3.3.2 inclusion criterion 6
Description of change		Clarification as a footnote to the inclusion criterion itself that if the CCT run-in compliance threshold (i.e. at least 2 hours per week for two weeks, totalling 4 hours CCT) is not met, then the patient may still be randomized pending a documented discussion between the investigator and the CTM or CTL
Rationale for change		Alignment with existing wording in Section 4.3
Section to be changed		3.3.2 inclusion criterion 7
Description of change		Remove specific mention of at-home CCT exercises
Rationale for change		Overlap with inclusion criterion 6 which pertains to patient's ability to comply with at-home CCT exercises
Section to be changed		3.3.3
Description of change		New exclusion criterion 29 for patients with known active infection with SARS-CoV-2 within the last 30 days prior to randomization
Rationale for change		Due to COVID-19 increased risk for study patients
Section to be changed		3.3.4.1
Description of change		Addition of additional criterion for discontinuation of trial treatment for patients that experience severe of serious symptomatic infection with SARS-CoV-2
Rationale for change		Due to possible increased risk of COVID-19 complications for patients taking BI 425809
Section to be changed		4.1.4
Description of change		Adjustment to repeated text in same section
Rationale for change		Remove unnecessary (repeated) text

Section to be changed		4.1.4
Description of change		Added clarification that split visits are to be done on 2 consecutive calendar days
Rationale for change		Avoid the possible misinterpretation of the word "sequential" that could lead to a split visit being done a Friday and the following Monday
Section to be changed		4.1.4
Description of change		Including the possibility for trial medication to be shipped from the site to the patient if necessary due to the COVID-19 pandemic
Rationale for change		Allow patients that cannot visit the site due to COVID-19 to continue on trial medication if judged favourable and safe by the investigator
Section to be changed		4.2.1
Description of change		Added the word "only" when describing patient's use of their current antipsychotic and concomitant psychotropic medications during the trial
Rationale for change		Additional clarity that new antipsychotic and psychotropic medications are discouraged during the treatment period
Section to be changed		4.2.1
Description of change		Added instructions that CCT run-in during screening period should stop once eligibility is confirmed
Rationale for change		Limit CCT exposure prior to baseline (Visit 2)
Section to be changed		4.2.2.1
Description of change		Added text that if patients take antihistaminic, benzodiazepine or other sedative medication less than 8 hours before MCCB, then the visit should preferably (if possible) be rescheduled within the allowed visit window
Rationale for change		Suggested process to avoid patients completing MCCB within 8 hours of taking antihistaminic, benzodiazepine or other sedative medication
Section to be changed		5.1
Description of change		Add that SCoRS will be done at screening (Visit 1)
Rationale for change		Alignment with FLOW CHART
Section to be changed		Table 5.2.3: 1
Description of change		Remove (Stix) from Urinalysis category
Rationale for change		Correction; on-site dipstick (stix) is not being used for the indicated urinalysis tests
Section to be changed		5.2.6.2
Description of change		Define the individual patient´s end of study as the Follow-up Visit
Rationale for change		Clarification, in alignment with FLOW CHART footnote (*****)

Section to be changed		5.2.6.2
Description of change		Remove the requirement to use fax when sending BI SAE form
Rationale for change		Some sites may not have access to fax and can use another method to send SAE form to BI
Section to be changed		5.2.6.2
Description of change		Additional note that any hemoglobin decrease >20 g/L (2 g/dL) since baseline (Visit 2) or leading to symptoms of anemia (e.g. dyspnea, dizziness, etc) will require safety follow-up with safety lab at the next visit(s), or earlier if considered necessary by the investigator
Rationale for change		New safety information regarding risk of hemoglobin decrease
Section to be changed		6.2
Description of change		Change to more generic introductory wording for the various guidance points pertaining to conduct of the neuropsychological assessments
Rationale for change		Some points are required while others are preferred, so not accurate to characterize all points as requirements that need to be followed
Section to be changed		6.2
Description of change		Added clarification that split visits are to be done on 2 consecutive calendar days
Rationale for change		Avoid the possible misinterpretation of the word “sequential” that could lead to a split visit being done a Friday and the following Monday
Section to be changed		6.2
Description of change		Clarify that the CCT “coach”, not the patient, will need to create patient accounts within the [redacted]
Rationale for change		Only the CCT “coach”, and not the patient, is able to create patient accounts within the [redacted]
Section to be changed		6.2
Description of change		Mention potential modifications for trial conduct related in situations when patients might not be able to come to the site for the scheduled visit during the COVID-19 pandemic
Rationale for change		Adding reference to modifications described in Section 10.5
Section to be changed		6.2.1
Description of change		Add SCoRS as an assessment to be done during the screening period
Rationale for change		Alignment with FLOW CHART
Section to be changed		6.2.1

Description of change		Added instructions that re-screening must be registered in IRT
Rationale for change		To align with established procedures for registering re-screened patients in IRT
Section to be changed		6.2.2
Description of change		Added reminder (applicable to Visit 2 and as needed throughout the treatment period) that patients should avoid taking antihistaminic, benzodiazepine or other sedative medication within 8 hours of MCCB visits, if applicable
Rationale for change		Avoid patients completing MCCB within 8 hours of taking antihistaminic, benzodiazepine or other sedative medication
Section to be changed		6.2.2
Description of change		Added clarification that split visits are to be done on 2 consecutive calendar days
Rationale for change		Avoid the possible misinterpretation of the word "sequential" that could lead to a split visit being done a Friday and the following Monday
Section to be changed		6.2.3
Description of change		Additional note that all patients with hemoglobin drop below 100 g/L (10 g/dL) or absolute decrease >20 g/L (2 g/dL) since baseline (Visit 2) will need to be followed up post-end of study until value returns to baseline/normal value, or resolution (per investigator's judgment)
Rationale for change		New safety information regarding risk of hemoglobin decrease
Section to be changed		7.3.5
Description of change		Clarification that samples of patients who receive placebo treatment will not be analysed
Rationale for change		Bioanalysis of placebo samples is not necessary
Section to be changed		8.2
Description of change		Add text regarding the need for patients to provide consent to any modifications to trial conduct that may be required during the COVID-19 pandemic
Rationale for change		Ensure patient is made aware of and provides agreement for any modifications due to COVID-19
Section to be changed		10.5
Description of change		New section added describing potential modification of trial conduct in case of restrictions due to COVID-19, such as remote visits (by phone) and direct-to-patient trial medication shipment
Rationale for change		Guidelines for modifications to trial visits to be considered during COVID-19

APPROVAL / SIGNATURE PAGE

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Title: A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of BI 425809 once daily with adjunctive Computerized Cognitive Training over 12 week treatment period in patients with schizophrenia

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	22 Jul 2020 17:28 CEST
Author-Trial Clinical Pharmacokineticist		22 Jul 2020 21:04 CEST
Approval-Team Member Medicine		23 Jul 2020 09:25 CEST
Approval-[redacted] Medicine		23 Jul 2020 23:39 CEST
Approval-Biostatistics		24 Jul 2020 16:56 CEST
Approval-Clinical Trial Leader		28 Jul 2020 22:28 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed