Clinical Trial Protocol

	Document Number:	**c14883409-02**
EudraCT No.: **EU Trial No:**	2017-002369-23	
BI Trial No.:	1289-0049	
BI Investigational Product(s):	BI 409306	
Title:	A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 28-week treatment period as adjunctive therapy to antipsychotic treatment for the prevention of relapse in patients with schizophrenia.	
Lay Title:	This study tests whether BI 409306 prevents patients with schizophrenia from becoming worse. This study looks at how well patients tolerate BI 409306 and how effective it is over 6 months.	
Clinical Phase:	II	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Email: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted] Email: [redacted]	
Status:	Final Protocol (Revised Protocol based on global amendment 1)	
Version and Date:	**Version:**	**Date:**
	2.0	08 Nov 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 409306
Protocol date	21 Aug 2017
Revision date	08 Nov 2017
Trial number	1289-0049
Title of trial:	A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 28-week treatment period as adjunctive therapy to antipsychotic treatment for the prevention of relapse in patients with schizophrenia.
Coordinating Investigator:	[redacted] Phone: [redacted] Email: [redacted]
Trial site(s):	Multicentre trial
Clinical phase:	II
Objective(s):	To investigate the efficacy, safety and tolerability of BI 409306 25mg and 50mg once daily compared with placebo given for 28 weeks in patients with schizophrenia on antipsychotic treatment. The study is designed to show superiority of BI 409306 over placebo in preventing relapse of schizophrenia symptoms.
Methodology:	Multinational, multicentre, randomised, double-blind, placebo-controlled, parallel group study
Number of patients entered:	387
Number of patients on each treatment:	129 patients per treatment group
Diagnosis :	Patients with diagnosis of schizophrenia per International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)
Main in- and exclusion criteria	Male and female patients 18-55 years old with schizophrenia in the stable phase of illness on a stable antipsychotic medication regimen. Patients can be treated with no more than two

<table>
<tr><td></td><td>antipsychotic medications. Eligible patients will have experienced at least 2 relapses within the past 5 years or at least 1 relapse if they were diagnosed less than 3 years ago.</td></tr>
<tr><td>Test product(s):</td><td>BI 409306</td></tr>
<tr><td>dose:</td><td>10 mg, 25 mg or 50 mg

During 28 week treatment period: 25 mg or 50 mg q.d.

During 7 day withdrawal/taper period during week 29 (10 mg tablets):
<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="2">Treatment Group</th></tr>
<tr><th>25 mg q.d.</th><th>50 mg q.d.</th></tr>
<tr><td rowspan="7">Week 29</td><td>Day 1</td><td>20 mg</td><td>40 mg</td></tr>
<tr><td>Day 2</td><td>20 mg</td><td>30 mg</td></tr>
<tr><td>Day 3</td><td>20 mg</td><td>30 mg</td></tr>
<tr><td>Day 4</td><td>10 mg</td><td>20 mg</td></tr>
<tr><td>Day 5</td><td>10 mg</td><td>20 mg</td></tr>
<tr><td>Day 6</td><td>10 mg</td><td>10 mg</td></tr>
<tr><td>Day 7</td><td>10 mg</td><td>10 mg</td></tr>
</table></td></tr>
<tr><td>mode of administration:</td><td>p.o. (oral)</td></tr>
<tr><td>Comparator products:</td><td>Matching placebo</td></tr>
<tr><td>dose:</td><td>Not applicable</td></tr>
<tr><td>mode of administration:</td><td>p.o.</td></tr>
<tr><td>Duration of treatment:</td><td>28 weeks</td></tr>
<tr><td>Endpoints</td><td>Primary efficacy endpoint:
The primary endpoint is time to first relapse until study end (planned at 28 weeks). Time of relapse will be obtained by selecting the earliest date from any, or all of the following 6 criteria:
• Time to hospitalization (involuntary or voluntary admission), intensive outpatient therapy or use of home treatment, as an alternative to hospitalization, for decompensation of schizophrenia symptoms
• Time to an assessment on the Clinical Global Impressions - Severity (CGI-S) of ≥ 5 (markedly ill) and either:

- an increase on any of the following individual Positive and Negative Syndrome Scale (PANSS) items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content - to a score > 4 with an absolute increase of ≥2 on that specific item since randomisation
or</td></tr>
</table>

	- an increase on any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content -to a score > 4 and an absolute increase of ≥4 on the combined 4 PANSS items since randomisation or - PANSS total score increase of ≥25% relative to baseline score or an increase of ≥10 points if baseline score was ≤40 • Time to a prescription for a new antipsychotic or time to an increase in dose of an ongoing antipsychotic medication for significant worsening of schizophrenia symptoms • Time to clinically significant homicidal ideation, in the investigator's judgement • Time to suicidal behavior, or time to assessment of suicidal ideation type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) • Time to deliberate self-injury and/or violent behaviour resulting in suicide or in clinically significant injury to the patient or another person or property damage, in the investigator's judgement **Secondary efficacy endpoints:** <u>Key secondary endpoint:</u> • Change from baseline in Positive and Negative Symptom Score (PANSS) positive symptoms score after 28 weeks of treatment. • <u>Secondary endpoints:</u> • Time to new prescription or increase in dose of an ongoing antipsychotic medication. • Change from baseline in Clinical Global Impressions–Severity (CGI-S) scale score after 28 weeks of treatment. • Patient Global Impressions-Improvement (PGI-I) scale score after 28 weeks of treatment. • Suicidal ideation and behaviour as assessed by C-SSRS after 28 weeks of treatment. • Change from baseline in Personal and Social Performance scale (PSP) score after 28 weeks of treatment.
Safety criteria:	Physical examination, vital signs, laboratory tests, electrocardiogram (ECG), suicidality, extrapyramidal symptoms, and occurrence of serious and non-serious adverse events will be assessed.
Statistical methods:	For the primary endpoint of time to relapse, the equality of the hazard rates will be tested by the Wald test for the treatment effect in a stratified Cox proportional hazards model. The model includes treatment as the only covariate and is stratified by country.

	Secondary endpoints will be analysed descriptively using relative risk ratios and 95% confidence intervals.

FLOW CHART

																				Completed Patients		Early D/C Patients			All Patients
Trial Periods	**Screening Period[1]**	**Randomized Treatment Period**															**Withdrawal/ Taper[2]**			**Follow-up**		**Early D/C Option 1**	**Early D/C Options 2-4**		**End of Study**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**EOT[3]**	**F/U[4]**	**EOT[3]**	**EOT[3]**	**F/U[5]**	
Study week	**-4**		**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**				**29**	**32**				
Study day	**-28**	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	V16 +2	V16 +4	V16+7		V16+28			EOT +28 days	
Visit window in days	-28 to -7	N/A	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-1	+/-1	+/-1		+/-3			+/-3	
Informed consent[6]	X																								
Demographics	X																								
Medical history	X																								
Physical examination	X															X							X		
Vital signs	X	X		X		X		X		X		X		X		X	X	X	X		X	X	X	X	
Height	X																								
Weight	X							X								X					X	X	X	X	
Pregnancy test (urine; females only)[7]	X	X		X		X		X		X		X		X		X			X				X		
12 lead-ECG[8]	X							X								X							X		
Safety laboratory tests (urine/blood)[9]	X	X						X				X				X			X		X	X	X	X	
Antipsychotic medication assessment in plasma[10]	X							X				X				X							X		
Pharmacokinetic sampling (BI 409306)[11]		X						X								X									
Urine drug screen	X																								
Pharmacogenomic sampling[12]	X	X																							
Optional DNA biobanking (requires separate ICF)[13]		X																							
Mini-international neuropsychiatric interview (M.I.N.I.)	X																								
In-/Exclusion Criteria	X	X																							
Randomization		X																							
Phone Visit[14]			X		X		X		X		X		X		X										

FLOW CHART (Cont.)

																				Completed Patients		Early D/C Patients			All Patients
Trial Periods	**Screening Period[1]**	**Randomized Treatment Period**															**Withdrawal/ Taper[2]**			**Follow-up**		**Early D/C Option 1**	**Early D/C Options 2-4**		**End of Study**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**EOT[3]**	**F/U[4]**	**EOT[3]**	**EOT[3]**	**F/U[5]**	
Study week	**-4**		**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**				**29**	**32**				
Study day	**-28**	1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	V16 +2	V16 +4	V16+7		V16+28			EOT +28 days	
Visit window in days	-28 to -7	N/A	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-1	+/-1	+/-1		+/-3			+/-3	
Clinical Global Impressions -Severity (CGI-S)	X	X		X		X		X		X		X		X		X							X		
Clinical Global Impressions-Improvement (CGI-I)												X				X							X		
Patient Global Impressions –Improvement (PGI-I)												X				X							X		
[redacted]																									
Personal and Social Performance scale (PSP)		X														X							X		
Positive and Negative Syndrome Scale (PANSS)	X	X		X		X		X		X		X		X		X					X	X	X	X	
[redacted]																									
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Interactive Response Technology (IRT) Use[15]	X	X		X		X		X		X		X		X		X				X		X	X		
Dispense study drug		X		X		X		X		X		X		X		X[16]									
Smartphone app training, set-up/ In-clinic drug administration		X																							
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Compliance check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X		
Termination of trial medication																				X		X	X		
Trial Completion																									X
Vital Status[17]																									X

1. Screening Visit procedures are not required to be completed on the same day.
2. Patients will be randomised to either abrupt withdrawal or slow taper of study drug for 7 days. Vital signs, suicidality and adverse events will be closely monitored during this period.
3. End of Treatment (EOT) for patients who complete the treatment and withdrawal/taper periods will be completed at Visit 19. Patients who discontinue study drug prematurely should ideally be observed until study end as if they were still receiving blinded study treatment. There are 4 options for observing patients after premature drug discontinuation. Sections 3.3.4.1 and 6.2.2 and 6.2.2.1 provide additional information.

   Early Discontinuation (D/C) Option 1: An EOT Visit must be conducted within 7 days of the last dose of study medication for patients who agree to conduct regularly scheduled visits after premature drug discontinuation. Thereafter, patients should be followed up according to the regular visit schedule. Visit 16 will be the final visit for patients choosing this Early D/C Option.

   Early D/C Options 2-4: An EOT Visit must be conducted within 7 days of the last dose of study medication for patients who agree to conduct the remaining visits over the phone, or patients who agree to be contacted or data collected via alternative sources approximately 28 weeks after the patient was randomised.
4. Patients who complete the treatment and withdrawal/taper periods will be scheduled for a Follow-Up Visit 28 days after Visit 16. Patients who enter the withdrawal/taper period, but discontinue taking their study drug will have a Follow-up Visit as planned at Week 32.
5. Patients who prematurely discontinue study medication and choose Early D/C Option 1 do not need a Follow-Up Visit if they discontinued >4 weeks prior to Visit 16. If a patient choosing Early D/C Option 1 discontinues <4 weeks prior to Visit 16, a Follow-up Visit will be performed 28 days after the EOT Visit. Patients who prematurely discontinue study medication and choose Early D/C Options 2-4 will have a Follow-Up Visit performed 28 days after the EOT visit. See Sections 3.3.4.1, 6.2.2, and 6.2.2.1.
6. Written informed consents for main study and optional pharmacogenomics test for deoxyribonucleic acid (DNA) banking must be obtained before any study-related procedures and assessments are performed. The registration of patients for the study is through the Interactive Response Technology (IRT). Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's and Institutional Review Board (IRB)/ Independent Ethics Committee's (IEC) instructions.
7. Female patients of childbearing potential must perform urine (dipstick) pregnancy test at Visits 1 through EOT.
8. A 12-lead electrocardiogram (ECG) is to be performed during the scheduled visits or within 24 hours prior to the visit, except for Visit 1 (Screening Visit), where the ECG test will be performed only after a written informed consent for the main study has been obtained.
9. Routine laboratory tests are hematology, chemistry, coagulation, and urinalysis as described in Table 5.2.3:1. Patients should be fasting for at least 8 hours prior to blood samples collection, except at Visit 1.
10. Blood samples will be collected to check the presence of antipsychotic medication(s) in plasma. A sample should also be collected at the time a relapse is diagnosed.
11. Pharmacokinetic samples will be collected to measure BI 409306 and its two metabolites CD 13896 and CD 14084. See Sections 5.3 and 10.1 for details.
12. One blood sample will be taken at screening visit for genotyping of CYP2C19 from all patients taking medication known to be strong or moderate inhibitors of CYP1A2. One additional blood sample for genotyping of genes involved in absorption, distribution, metabolism and elimination will be collected preferably at Visit 2. However, collection of this sample at later visits is permitted.
13. Collection of a sample for DNA biobanking is optional (See Section 5.4.1 for more details). Participating patients are required to give informed consent specifically for biobanking. DNA biobanking requires only one blood sample to be taken, preferably at Visit 2 (Randomisation). However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.
14. Interim phone visits are scheduled to assess the overall status of the patient, check compliance, and to collect new AE and concomitant medication information. If symptom worsening is suspected, an unscheduled in-clinic visit should be scheduled. See Section 6.2.2. Columns are shaded in grey in the Flow Chart to indicate phone visits.
15. The study staff must utilize the Interactive Response Technology (IRT) for entering the patient into the system for screening, randomisation, and study medication allocation and tracking.
16. Patients who complete the 28 week treatment period will be dispensed a one-week wallet for the withdrawal/taper period.
17. Patients who have prematurely discontinued study drug and have not continued making regular visits (in person or phone) must have Vital Status collected approximately 28 weeks after the patient was randomised.

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ABBREVIATIONS

AD	Alzheimer's disease
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	
ALT	Alanine aminotransferase (SGPT)
APS	Attenuated Psychosis Syndrome
AST	Asparatate aminotransferase (SGOT)
BI	Boehringer Ingelheim
BLQ	Below the limit of quantification
bpm	Beats per minute
CA	Competent Authority
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
cGMP	Cyclic guanosine monophosphate
CIAS	Cognitive impairment associated with schizophrenia
Cmax	Maximum concentration
CML	Clinical Monitor Local
Cpress	Residual concentration in plasma
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electrocic (sometimes referred to as "eCRF")
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
D/C	Discontinuation
DDI	Drug-drug interaction
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
EDC	Electronic Data Capture
EM	Extensive metabolizers
EOT	End of treatment
[redacted]	
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
[redacted]	

IB	Investigator's Brochure
IC 50	Half maximal inhibitory concentration
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intent to Treat
IUD	Intrauterine device
IUS	Intrauterine hormone releasing systems
LTP	Long term potentiation
MCCB	MATRICS Consensus Cognitive Battery
MedDRA	Medical Dictionary for Regulatory Activities
M.I.N.I.	Mini-international neuropsychiatric interview
NMDA	N-methyl-D-aspartate
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
OPU	Operative Unit
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PD	Pharmacodynamics
PDE9	Phosphodiesterase-9
PGI-I	Patient Global Impressions –Improvement
PI	Principal Investigator
PK	Pharmacokinetics
PM	Poor metabolizers
p.o.	per os (oral)
PSP	Personal and Social Performance scale
PTM	Planned time
q.d.	quaque die (once a day)
REP	Residual Effect Period
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TS	Treated set
ULN	Upper limit of normal
URS	User requirement specifications
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

BI 409306 is a Phosphodiesterase-9 (PDE9) inhibitor under development for the treatment of Alzheimer's disease (AD), reduction of relapse in patients with schizophrenia, and prevention of first episode of psychosis in patients with attenuated psychosis syndrome (APS) [c01694347-09].

1.1 MEDICAL BACKGROUND

Schizophrenia is a chronic and disabling illness affecting approximately 1% of the population, with the majority of patients experiencing multiple relapses during the course of the illness. Relapse can be assessed in many ways, however regardless of characterization it is clear that acute psychotic exacerbation in these individuals has serious negative consequences, including a risk of patients harming themselves or others, of jeopardizing personal relationships, education or employment status, and of further stigmatization of the illness. As well, relapse has been posited to incur biological risk in that active psychosis may reflect actual disease progression such that patients may not recover their previous level of function and treatment refractoriness may emerge [R15-1782].

Multiple factors likely contribute to incurring risk of relapse. Most prominently, in a meta-analysis of longitudinal studies it was found that non-adherence with medication significantly increased the risk for relapse after first-episode psychosis. In a prospective, 5 year follow-up of first-episode psychosis patients it was found that the most common risk factor was antipsychotic medication discontinuation. Besides this explanation, substance abuse or other reasons for relapse (called natural or primary) clearly exist which include stress, diminished resilience, hormonal or immunological problems. Irrespective of etiology, psychosis relapse is postulated to be accompanied with or due to, a hyperdopaminergic state [R17-0970].

In clinical settings withdrawal from treatment is common, especially in the early stages of illness. In the CATIE study, a well-designed “real-world” trial, it was found that 74 percent of patients discontinued the study medication before 18 months leading the authors to note “Only a minority of patients in each group took their assigned drug for the duration of phase 1 (rates of discontinuation ranged from 64 to 82 percent). This outcome indicates that antipsychotic drugs, though effective, have substantial limitations in their effectiveness in patients with chronic schizophrenia” [R12-3534].

Therefore, despite the clearly demonstrated benefits of antipsychotic therapy in relapse prevention, ongoing maintenance treatment carries its own burden, including substantial risk of relapse, significant side-effects and even the possibility of brain morphological changes.

In recognition of the associated risks with disease exacerbation, improving medication adherence and relapse prevention have been emphasized as key components of the management of schizophrenia.

Given the difficulties in identifying those at risk of relapse, the ineffectiveness of rescue medications in preventing full-blown psychotic recurrence and the potentially serious conse-

quences, every effort needs to be made to provide effective options beyond adherence-supporting strategies alone.

1.2 DRUG PROFILE

BI 409306 is a new chemical entity (NCE) intended for oral administration. Film coated immediate release tablets of 10mg, 25 mg and 50mg will be applied in this trial.

Non-clinical Summary

In vitro and in vivo non-clinical pharmacological studies were performed to determine potency, selectivity and efficacy of BI 409306 in cellular and animal models. In brief, BI 409306 is a potent and selective PDE9 inhibitor. It enhances long term potentiation (LTP) in rat hippocampal slices indicating improvement of cellular processes crucial for memory formation, and it increases cyclic guanosine monophosphate (cGMP) levels in rat brain indicating target engagement in vivo. In vivo proof-of-concept regarding memory enhancement/improvement could be achieved in two rodent cognition models addressing working memory and recognition memory domains (for details please refer to Section 5.1 of the Investigator's Brochure (IB) [c01694347-09])

Standard non-clinical in vitro and in vivo studies on drug metabolism and pharmacokinetics (PK) were performed including studies for the identification of drug metabolizing enzymes, cytochrome inhibition and induction, involvement of transporters, permeability studies, pharmacokinetics and metabolism studies in animals and whole body autoradiography in rats (Section 5.2 of the Investigator's Brochure (IB) [c01694347-09].

BI 409306 was tested in a comprehensive panel of in vitro and in vivo General Pharmacology tests (non- Good Laboratory Practice (GLP)) and in the core battery of Safety Pharmacology tests (GLP). The major findings were cardiovascular effects which were similar to those described for other PDE inhibitors and considered to be secondary to a cGMP related vasodilatation. Repeat-dose oral toxicity studies were conducted with daily oral (gavage) administration of BI 409306 to mice, rats, and dogs for up to 13 weeks. Target organs identified in these studies were the cardiovascular system (rats and dogs), liver (rats), adrenal glands (rats), ovaries (rats), and spleen (rats). Adverse effects in rats were mainly limited to the highest dose tested. Only an adaptive finding in the adrenal glands of rats interpreted as being secondary to the cardiovascular effects occurred at lower dose levels. Cardiovascular effects in dogs occurred also at lower doses but can be monitored in clinical trials. Chronic toxicity studies in rats and dogs are ongoing. The genotoxicity profile of BI 409306 was tested in the standard battery of genotoxicity tests and a comet-assay in rats. The overall assessment revealed that BI 409306 is not genotoxic. BI 409306 was not teratogenic in rats and rabbits and, based on preliminary results, did not alter the fertility and early embryonic development in rats [c01694347-09].

Clinical Summary

In all 12 healthy volunteer trials, the most frequent drug related adverse events were visual side effects that occurred shortly after dosing, mostly resolved within 1 h, i.e., in close

connection to maximum BI 409306 plasma concentrations, as the concentration-time profile sharply and steeply peaks within the first 1-2 hours and then rapidly declines afterwards. Overall, there were no relevant changes observed for laboratory, electrocardiogram (ECG) recordings, and vital signs following treatment with BI 409306 when compared to placebo. Only a rapid and short lasting increase in supine pulse rate of 12.5 ± 2.7 beats per minute (bpm) was reported in Chinese CYP2C19 poor metabolizers subjects treated with BI 409306 (100 mg single dose) in study 1289.4. Following this observation, pharmacometric analysis of all available human data revealed a BI 409306 plasma concentration dependent increase in supine pulse rate in typical subjects reaching a maximum of 7-13 bpm (median) at the high exposure end in CYP2C19 poor metabolizers treated with BI 409306 at 100 mg. The maximum effects of BI 409306 on pulse rate were generally achieved at maximum BI 409306 plasma concentrations (20-30 minutes post dose) and disappeared rapidly with declining concentrations [c01694347-09]. The effects of BI 409306 on pulse rate were further examined in healthy male volunteers under resting and exercise conditions following single oral doses of 50 and 200 mg [c03808525-01]. In line with previous results, heart rate profiles closely correlated with drug systemic exposure profiles and the heart rate increase was 11.51 bpm at the maximum individual plasma concentration measured during exercise.

Altogether, good to satisfactory safety and tolerability were observed in single doses of BI 409306 (up to 350mg in CYP2C19 extensive metabolizers (EM); up to 100mg in CYP2C19 poor metabolizers (PM)) in healthy young volunteers and multiple doses (14 days up to 100mg EM/50mg PM) of BI 409306 in healthy young and elderly subjects. In addition data from completed studies demonstrate that the increase in heart rate was transient, closely related to the time of maximum drug concentrations, and of low amplitude [c01694347-09].

Study 1289.18 was conducted to assess safety, tolerability, PK and pharmacodynamics (PD) of BI 409306 25 mg, 50 mg, or 100 mg once a day (q.d.) for 14 days in patients with mild-to-moderate schizophrenia. Satisfactory safety and tolerability were observed while PK mirrored that of healthy volunteers. Recently completed study 1289.6 (proof of concept study in patients with cognitive impairment associated with schizophrenia (CIAS)) failed to achieve the primary endpoint of improving cognition as assessed by the MATRICS Consensus Cognitive Battery (MCCB), however demonstrated acceptable safety and tolerability at all doses. The percentage of subjects with any AE increased with increasing BI 409306 dose, ranging from 33.3% in the 10 mg group to 53.5% in the 100 mg group. The incidence of AEs in the 10 mg and 25 mg dose groups was similar to that of the placebo group. Most AEs were mild or moderate in intensity, with only 2 subjects in the BI 409306 groups and 4 subjects in the placebo group experiencing severe adverse events (AEs). Most striking was the finding that Serious AEs (SAEs), including 8/8 psychiatric SAEs, were only reported in the placebo group vs. none in the active arms. Further, it was noted that results of the C-SSRS showed suicidal ideation was reported in no subjects in the 10 mg group, 1 subject (1.2%) in the 25 mg group, 2 subjects (2.5%) in the 50 mg, 1 subject (1.2%) in the 100 mg group, and 6 subjects (3.6%) in the placebo group. It was further noted that the severity of the suicidal ideation present was more severe within the placebo subjects, with 3 placebo subjects reporting “Active suicidal ideation with any methods (not plan) without intent to act” and one subject reporting “Active suicidal ideation with some intent to act, without specific plan” vs. zero such findings in the active dose groups [c01694347-09; c09340078-01].

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

For a more detailed description of the BI 409306 profile, including pharmacokinetics and pharmacodynamics, please refer to the current Investigator's Brochure (IB) [c01694347-09].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The etiology of schizophrenia is believed to originate from abnormalities in brain development which are linked to an insult to the brain in fetal development. In addition, susceptibility genes for schizophrenia linked to synaptogenesis and neuronal connectivity may contribute to such abnormal brain development. These disturbances manifest into abnormalities of dopaminergic and glutamatergic circuits after completion of brain development, i.e at beginning of adulthood. Thus, these abnormalities are considered to be the pathophysiological basis of positive, negative and cognitive symptoms in patients with schizophrenia [P17-01959, R17-0563]. More specifically, negative and cognitive symptoms (e.g. social withdrawal, flat affect or memory impairment) are believed to be a consequence of hypoactivation of the meso-cortical dopamine pathway and/or excitatory-inhibitory imbalance of indirect cortico-cortical glutamate circuits. Positive symptoms, i.e. psychosis, seem to be caused by hyperactivation of the meso-limbic dopamine pathway due to hyperactivation of the cortico-brainstem glutamate pathway and/or by increased cortical activation induced by reduced thalamic inhibition (filtering) due to meso-limbic dopamine hyperactivation (i.e. dysfunction of cortico-striatal-thalamic-cortical loop) [P17-01959, R17-0563]. In the course of the illness most patients with schizophrenia experience multiple relapses which are characterized by acute psychotic exacerbation associated with striatal dopamine hyperfunction [R17-0972, R17-0973]. Hence, psychosis represents a state of aberrant salience due to a dysregulated hyperdopaminergic state, and accordingly, current antipsychotics do not eradicate psychotic symptoms but dampen them [R17-0970, R17-0969]. There are manifold explanations for relapse in patients under antipsychotic medication. One would be interventional or secondary relapse due to antipsychotic non-adherence and/or substance abuse, another one would be natural or primary relapse due to stress, diminished resilience, hormonal or immunological problems [R17-0971]. By both ways, psychosis relapse would be accompanied with or due to a hyperdopaminergic state as shown e.g. in a study applying a psychosocial stress task to patients with schizophrenia [R16-1601].

Due to the functional interaction of the dopaminergic with the glutamatergic system in the pathophysiology of schizophrenia, it is plausible that an approach which aims at ameliorating the dysfunctional glutamatergic system in schizophrenia such as PDE9 inhibition [c01694347-09], might also represent a viable approach for prevention of relapse or reduction of symptoms associated with exacerbation in patients with schizophrenia. Clinical support for this is found in the results of the completed 1289.6 phase 2 proof of concept trial with BI 409306 assessing treatment of cognitive impairment associated with schizophrenia in which a striking imbalance (100% vs.0%) of SAEs of psychiatric worsening in the placebo arm vs. none in any active arm occurred [c09340078-01]. Further support for this idea arises from published preclinical animal studies evaluating the effect of PDE9 inhibition in rodent models related to the meso-limbic dopamine pathway and cortico-striatal-thalamic-cortical loop. In

these animal experiments, it has been shown that the PDE9 inhibitor PF-4447943 potentiated the effect of the antipsychotic drug risperidone on prepulse inhibition and improved auditory gating deficits induced by a hyperdopaminergic state, but it did not show relevant antipsychotic-like effects in the amphetamine-induced hyperlocomotion test [R16-2785]. This clearly indicates that PDE9 inhibition is able to ameliorate a hyperdopaminergic state based on functional interaction within the cortico-striatal-thalamic-cortical loop/circuit (prepulse inhibition and auditory gating tests), but not meso-limbic dopamine pathway (hyperlocomotion test). As described above, dysfunction of both pathways/circuits - alone or together - are crucially involved in the pathophysiology of positive symptoms of schizophrenia (i.e. psychosis). Therefore, PDE9 inhibition as add-on to antipsychotic treatment would represent a novel therapeutic approach for reduction of disease relapse.

Taken together, these preclinical and clinical findings suggest that inhibition of PDE9 by BI 409306 represents a rational approach for reduction of disease relapse via ameliorating the hyperdopaminergic state of the cortico-striatal-thalamic-cortical circuit considered to play a crucial role in psychosis.

The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event, and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

Overall, BI 409306 shows a favorable nonclinical safety profile. There was no genotoxic potential of BI 409306. The toxicological profile of BI 409306 is characterized by cardiac effects which seem to be consistent with those described for phosphodiesterase inhibitors in general. Previous clinical trials found that BI 409306 was well tolerated in young and elderly healthy subjects in single doses of 0.5 to 350 mg and multiple doses up to 100 mg once daily. Data from the recently completed 1289.6 trial in 518 subjects with schizophrenia demonstrated AEs for 10mg and 25mg to be in the range of placebo. The most frequent drug related adverse events reported in all trials were visual side effects that occurred shortly after dosing and mostly resolved within 1 hour [c09340078-01]. A dedicated ocular safety study demonstrated no relevant changes to ocular parameters [c09168615-01] and a dedicated cardiovascular safety study found exercise testing did not suggest a clinically relevant impact on heart rate or cardiac function [c03808525-01]. All adverse effects generally were restricted to doses 100 mg or higher and were reversible [U12-1034-01; U13-1182-01; U12-2165-01; U13-1303-01]. Cardiac function will be monitored during the study according to the Flow Chart.

No effect on dopaminergic systems in pharmacological models has been noted and no adverse effects on glucose homeostasis have been seen (as seen with neuroleptics used off-label in this population). Drug-drug interaction (DDI) identified to date suggests potential liability for CYP2C19 poor metabolizers if medication inhibiting CYP1A2 is co-administered

with BI 409306, and for CYP2C19 non-poor metabolizers if the patient is concomitantly taking medications that inhibit both CYP1A2 and CYP2C19. However, this can be monitored and managed in this population [c01694347-09].

Although neither teratogenic, nor effect on fertility and early embryonic development has been seen in toxicology studies, no studies have been done with BI 409306 in pregnant women or women who are nursing their infants. It is unknown if BI 409306 is safe for pregnant women, unborn babies and infants who are nursing. It is unknown either if BI 409306 has an effect on sperm or eggs [c01694347-09].

Hence, female patients who are nursing or pregnant are not allowed to join the study. Patients who are of child-bearing potential must accept to use a highly effective form of birth control throughout the trial and follow-up period.

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

This is an experimental drug and therefore an individual benefit cannot be guaranteed. Given the acceptable safety profile in nonclinical and toxicology studies, the good tolerability in the clinical trials completed to date, and the careful monitoring planned during the study visits, the sponsor feels the risk to the participating patients is minimized and balanced by a potential benefit due to the intensive medical care received. Patients randomised to the placebo arm will continue to receive standard of care treatment. Even if there is no direct benefit for the patients during participation in this trial, it can be assumed that the trial results may contribute to better drug development in the future for this unmet medical need.

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.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The objective of the study is to investigate the efficacy, safety and tolerability of BI 409306 25mg and 50mg once daily compared with placebo given for 28 weeks in patients with schizophrenia on antipsychotic treatment. The study is designed to show superiority of BI 409306 over placebo in preventing relapse of schizophrenia symptoms.

2.1.2 Primary endpoint(s)

The primary endpoint is time to first relapse until study end (planned at 28 weeks). Time of relapse will be obtained by selecting the earliest date from any, or all of the following 6 criteria:

- Time to hospitalization (involuntary or voluntary admission), intensive outpatient therapy or use of home treatment, as an alternative to hospitalization, for decompensation of schizophrenia symptoms

- Time to an assessment on the Clinical Global Impressions - Severity (CGI-S) of ≥ 5 (markedly ill) and either:

  - an increase on any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content - to a score > 4 with an absolute increase of ≥2 on that specific item since randomisation

  or

  - an increase on any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content - to a score > 4 and an absolute increase of ≥4 on the combined 4 PANSS items since randomisation

  or

  - PANSS total score increase of ≥25% relative to baseline score or an increase of ≥10 points if baseline score was ≤40

- Time to a prescription for a new antipsychotic or time to an increase in dose of an ongoing antipsychotic medication for significant worsening of schizophrenia symptoms

- Time to clinically significant homicidal ideation, in the investigator's judgement

- Time to suicidal behavior, or time to assessment of suicidal ideation type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS)

- Time to deliberate self-injury and/or violent behaviour resulting in suicide or in clinically significant injury to the patient or another person or property damage, in the investigator's judgement

2.1.3 Secondary endpoints

Key secondary endpoint:

- Change from baseline in Positive and Negative Symptom Score (PANSS) positive symptoms score after 28 weeks of treatment.

Secondary endpoints:

- Time to new prescription or increase in dose of an ongoing antipsychotic medication.
- Change from baseline in Clinical Global Impressions–Severity (CGI-S) scale score after 28 weeks of treatment.
- Patient Global Impressions-Improvement (PGI-I) scale score after 28 weeks of treatment.
- Suicidal ideation and behaviour as assessed by C-SSRS after 28 weeks of treatment.
- Change from baseline in Personal and Social Performance scale (PSP) score after 28 weeks of treatment.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multicentre, multinational, randomised, double-blind, placebo-controlled parallel group trial. In total, 387 patients with schizophrenia are planned for randomisation in this study.

Patients are included in the study once informed consent has been signed. Patients suitable after screening will be randomised to the 28 week treatment period assigned at a ratio of 1:1:1 to one of three treatment arms as shown in Figure 3.1: 1. After completion of the treatment period, patients will enter the 7 day withdrawal/taper period and then be scheduled for a follow-up visit. Randomisation into the withdrawal/taper period will be done up front, with patients from each treatment arm being randomised to withdrawal or taper in a 1:1 ratio. The randomisation will be stratified by country.

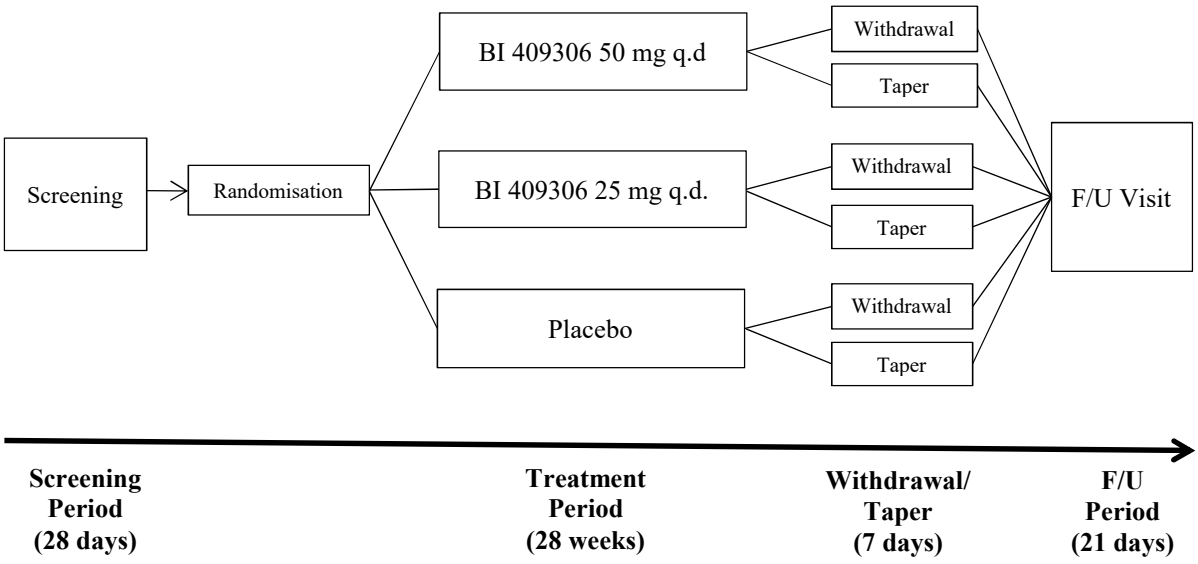


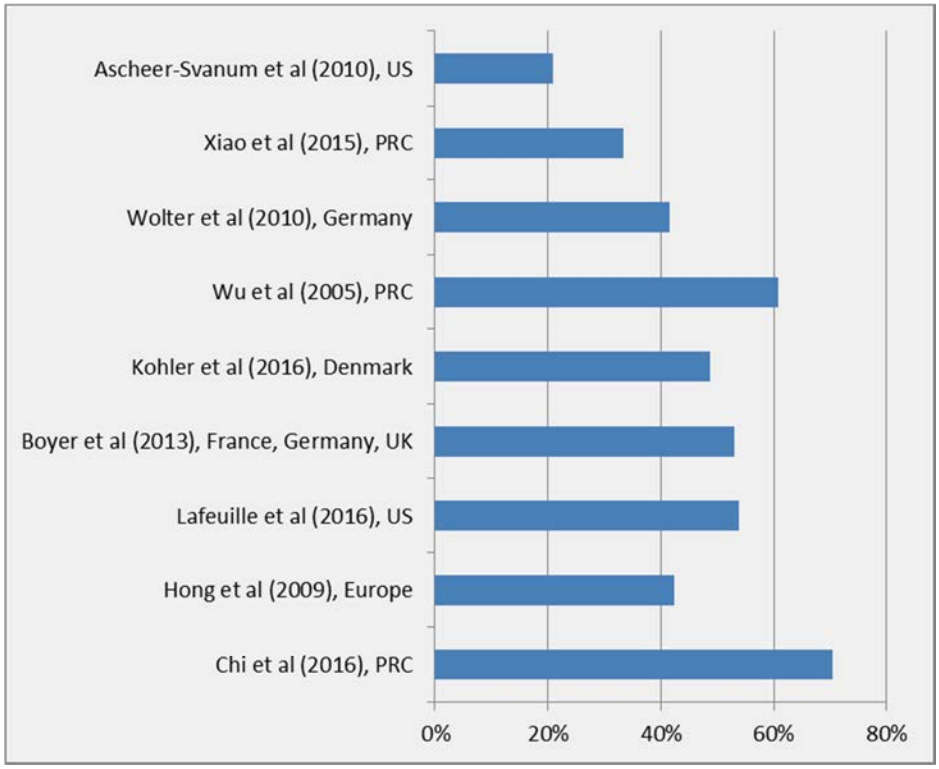
Figure 3.1: 1 Overview of trial design

The primary treatment comparison will be BI 409306 25 mg q.d. and 50 mg q.d. combined vs. placebo. Please refer to Sections 7.2 and 7.3.1 for the detailed analysis strategy.

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

A randomised, double-blind, parallel group design was chosen for this study to observe the effects of BI 409306 compared to placebo in preventing relapse of schizophrenia symptoms. The primary efficacy analysis is planned to be conducted after 28 weeks of treatment. A review of the literature illustrates wide variability in relapse rates in schizophrenia over 12 months (e.g. 20.9% to 60.8%) [See Figure 3.2: 1]. Possible reasons for variability in relapse rate include variations in definition of relapse utilized, differences in study population (e.g. outpatients vs. inpatients), differences in study methodology (e.g. different modes of data collection), and different study periods and treatment settings.

Figure 3.2: 1 Relapse Rates Reported in the Literature



PRC = Peoples Republic of China
[R17-2079; R17-2083; R17-2075; R17-2735; R17-2082; R17-2081; R17-2077; R17-2080; R17-2078]

The 28 week treatment period selected for this trial in combination with inclusion/exclusion criteria is expected to result in a population likely to experience relapse somewhere in the middle of this range, and is felt to be a reasonable study duration for a phase II study. Specifics regarding the power calculation and range of effect sizes covered are provided in Section 7.7.

Patients will be randomised to either abrupt withdrawal or slow taper of study drug for 7 days after the 28 week treatment period to monitor for signs and symptoms of withdrawal. Vital signs, suicidality and adverse events will be closely monitored during this period. The

proposed post-treatment follow-up period is considered to be sufficient for the pharmacodynamic effect of BI 409306 to discontinue and allow for assessment of reversibility of any unexpected adverse effects.

There is currently no approved medication specifically indicated for the prevention of relapse of schizophrenia symptoms as adjunctive treatment to antipsychotics. Since there is not an approved comparator available for this study, a placebo control group is being used in this study design. It should be noted that all patients, including those in the placebo group, are permitted to remain on other non-excluded psychotropic medications. The risk to the control group is discussed in Section 1.4.

3.3 SELECTION OF TRIAL POPULATION

It is planned that approximately 50 trial centres in 4 countries will be participating in this trial to randomise 387 patients.

It is expected that approximately 8 patients will be randomised at each trial centre. If enrolment is delayed, additional centres may be recruited.

To avoid differential centre influence on study results, permission to randomise more than 20 patients per site must be obtained from the Trial Clinical Monitor (TCM).

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

Patients who fail screening may repeat the screening phase once after discussion between the investigator and sponsor, provided that the reason for screen failure was reversible and has resolved. Permission to rescreen patients must be obtained from the TCM or Clinical Monitor Local (CML), and documentation of approval filed in the Investigator Site File (ISF). Rescreened patients must be re-consented and be given a new patient number. All Visit 1 procedures must be repeated.

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

3.3.1 Main diagnosis for trial entry

Patients with an International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) diagnosis of schizophrenia will be the basis for trial entry.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. ICD-10 diagnosis of schizophrenia ≥ one year prior to randomisation.

2. Outpatients in the stable phase of illness, as assessed by the investigator after review of medical records or documented discussion with treating clinician.

3. Patients currently taking a stable dose of antipsychotic medication(s) for at least 12 weeks prior to randomisation.

4. Detectable level of current antipsychotic medication(s) in plasma from blood drawn at Visit 1 (unless no assay is available for the antipsychotic(s) currently prescribed).

5. Patients who have experienced at least 2 relapses within the past 5 years or at least 1 relapse if they were diagnosed less than 3 years ago. Relapse is defined as the patient having any of the following using the above number of relapses and time frames:
   - Hospitalization for psychosis (involuntary or voluntary admission), intensive outpatient therapy or use of home treatment as an alternative to hospitalization (verified via medical record).
   - Emergency Department visit for worsening schizophrenia symptoms (verified via medical record).
   - Deliberate self-injury and/or violent behaviour resulting in significant injury to another person or property (verified by police record or treating mental health provider written record or documented phone conversation).
   - Change in the patient's antipsychotic medication or increase in antipsychotic medication dosage due to worsening of schizophrenia symptoms (verified by pharmacy records or treating mental health provider written record or documented phone conversation).

6. CGI-S score ≤4 at Visits 1 and 2.

7. PANSS total score ≤80 and a score of ≤ 4 on individual PANSS items conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content at Visit 1.

8. Of full age (according to local legislation, usually ≥ 18 years) and ≤ 55 years at the time of informed consent.

9. Patients must have an identified informant who will be consistent throughout the study.

10. Patients who report living at the same address for the 3 months prior to randomisation.

11. Male or female patients.

- Female patients of childbearing potential[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Patients must agree to use birth control throughout the trial and for at least 28 days after treatment has ended. Acceptable methods of birth control include combined estrogen-progestin oral, intravaginal or transdermal contraceptives, progestogen-only oral, injectable or implantable contraceptives, intrauterine devices (IUDs), intrauterine hormone releasing systems (IUSs), bilateral tubal occlusion, vasectomized sexual partner, and complete sexual abstinence (if acceptable by local health authorities) is allowed when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Male patients who are able to father a child must be ready and able to be abstinent or use adequate contraception for the duration of study participation and for at least 28 days after treatment has ended.

12. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. If the patient has a legal representative, then this legal representative must give written informed consent as well.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal 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.

3.3.3 Exclusion criteria

1. Patients treated with more than two antipsychotic medications (including more than two dosage forms).
2. Patients who are currently being treated with clozapine, or who have been treated with clozapine in the past 5 years.
3. Patients with a categorical diagnosis of another current major psychiatric disorder per the Mini-international neuropsychiatric Interview (M.I.N.I.).
4. Homicidal behaviour (in the investigator's judgement) in the past 2 years.
5. Any suicidal behavior in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior).
6. Any suicidal ideation of type 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 3 months (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent).
7. In the judgment of the investigator, any clinically significant finding from the physical examination or laboratory value deviating from normal or any evidence of a clinically significant concomitant disease or any other clinical condition that would jeopardize a patient's safety while participating in the clinical trial.
8. Other known neurological diseases (including but not limited to any kind of seizures or stroke).

9. 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 or in situ carcinoma of uterine cervix.
10. Planned elective surgery requiring general anesthesia, or hospitalization for more than 1 day during the study period.
11. Significant history of drug or alcohol dependence or abuse (Substance Use Disorder as defined in DSM-5 or ICD-10) within the last six months prior to informed consent (Not including caffeine or nicotine).
12. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
13. Patients taking strong or moderate CYP1A2 inhibitors who are also a CYP2C19 Poor Metabolizer (PM). Patients taking medication known to be strong or moderate inhibitors of CYP1A2 must be prospectively genotyped to ensure they are not poor metabolizers of CYP2C19. (A list of CYP1A2 and CYP2C19 inhibitors can be found in the ISF).
14. Patients taking strong or moderate CYP1A2 inhibitors who are also taking concomitant strong or moderate CYP2C19 inhibitors. (A list of CYP1A2 and CYP2C19 inhibitors can be found in the ISF.)
15. Patients with a history of moderate to severe hepatic impairment (Child-Pugh B / C).
16. Patients with a history of moderate to severe renal impairment (Stage 3 – 5).
17. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
18. In the judgment of the investigator, inability of the patient to comply with the clinical trial procedures.
19. Currently enrolled in another investigational device or drug study, or less than 6 months from Visit 1 since ending another investigational device or drug study(s), or participation in > 2 investigational drug clinical trials in the past 2 years.
20. Previous randomisation in any BI 409306 study.

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see sections 3.3.4.1 and 3.3.4.2 below.

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomisation, as well as the explanation of the consequences of withdrawal.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and case report form (CRF).

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, without the need to justify the decision.
- The patient becomes pregnant during the trial. Patient will be followed up until birth or other termination of the pregnancy.
- The patient needs to take concomitant drugs that in the clinical judgment of the investigator interfere with the investigational product.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- The patient 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.

Every effort should be made by the site staff to encourage patients to remain in the study and on study drug if medically safe. Patients who prematurely discontinue study drug must complete the End of Treatment (EOT) procedures as described in the Flow Chart and Sections 6.2.2 and 6.2.3. Patients who discontinue study drug prematurely should ideally be observed until the end of the trial as if they were still receiving blinded study treatment. For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

Patients that are not actively taking study drug may be less motivated to adhere to the study visit schedule. Investigators and site staff should work to detect early signs of waning interest and readily present such patients with the following options to encourage continued participation:

Early D/C Option 1:	Continue to conduct regularly scheduled study visits.
Early D/C Option 2:	Conduct all remaining study visits over the phone. At the time of planned clinic visits, only the following assessments need to be conducted via phone: PANSS, CGI-S, C-SSRS, Adverse Events, Concomitant Therapy.
Early D/C Option 3:	Discontinue participation in remaining study activities but permit collection of the occurrence of psychiatric illness/relapse and vital status approximately 28 weeks after randomisation through the patient or alternative person designated by the patient (e.g., family, spouse, partner, legal representative, or physician).
Early D/C Option 4:	Same as Option 3 above, but with the possibility of collection of the occurrence of psychiatric illness/relapse and vital status approximately 28 weeks after randomisation through review of patient's medical information from alternative sources (e.g., doctor's notes, hospital records, etc.).

Patients will be asked to choose the most rigorous form of follow-up that they are willing to comply with. Patients who refuse all four of the above are considered to have fully withdrawn consent to participate in the study.

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.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment. Refer to Section 3.3.4.1 above.

If the patient fully withdraws consent for participation in the study, the study will end for that patient. The patient should stop taking study medication and should be asked to complete the EOT and Follow-up procedures as described in the Flow Chart and Sections 6.2.2 and 6.2.3. Completing these procedures is strongly recommended for the patient's safety.

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 Good Clinical Practice (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 409306, as a film-coated tablet, will be produced by Boehringer Ingelheim Pharma GmbH & Co. KG.

Each film-coated tablet contains 10 mg, 25mg or 50 mg BI 409306.

Eligible patients are randomly assigned to double blind treatment at a ratio of 1:1:1 for the 28 week treatment period. Patients will be randomised to either slow taper or abrupt withdrawal of study medication for 7 days after completing the 28 week treatment period.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1a Characteristics of the test products-BI 409306

Substance:	BI 409306
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg, 25 mg or 50 mg
Posology:	q.d.
Route of administration:	Oral

Table 4.1.1: 1b Characteristics of the test products-BI 409306 matching placebo

Substance:	Placebo matching 10 mg, 25mg and 50mg
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	N/A
Posology:	q.d.
Route of administration:	Oral

4.1.2 Selection of doses in the trial

Data from the recent 1289.6 trial in patients with schizophrenia indicate no serious AEs in any active dose group (10mg, 25mg, 50mg, and 100mg) [c09340078-01]. Recent preliminary pharmacometric modelling indicates that at the dose of 25 mg once daily (q.d.) in non-PM subjects, the expected therapeutic exposures in the cerebrospinal fluid (CSF) (1xIC50 (half maximal inhibitory concentration)) will be achieved in 49% of subjects and will lead to an increase of CSF cGMP ≥ 50% above the baseline over a 4 hour duration after dosing. For the 50 mg q.d., about 94% of subjects are expected to reach such a CSF exposure with a 5.9 hour duration of an increasing CSF cGMP ≥ 50% above the baseline, while for the 10 mg q.d., it is clearly sub-therapeutic. AE data suggest that these doses 25 and 50mg are well-tolerated, and similar to placebo. In line with the proposed mode of action, it is hypothesized that compounds which strengthen N-methyl-D-aspartate (NMDA) receptor signalling and LTP, exert improvement in vivo outlasting drug exposure, therefore, two doses are planned to maximize the therapeutic drug levels in plasma and brain/CSF while providing an acceptable level of tolerability.

4.1.3 Method of assigning patients to treatment groups

During Visit 2 eligible patients will be randomised to receive BI 409306 25 mg q.d. or 50 mg q.d. or placebo in a 1:1:1 ratio. Additionally, each patient will be randomised up front in a 1:1 ratio to their method of treatment discontinuation (withdrawal or taper).The assignments will occur in a blinded fashion via Interactive Response Technology (IRT) according to a randomisation plan.

An IRT will be used to screen and randomise eligible patients, perform subsequent drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. The investigator will receive all necessary instructions to access IRT from the Sponsor or chosen provider. Detailed IRT functions/procedures will be documented in the user requirement specifications (URS) mutually agreed to by the sponsor and the IRT vendor.

Note that the medication number is different from the patient number (the latter is assigned directly after informed consent is obtained). Site personnel will enter the medication number in the eCRF.

4.1.4 Drug assignment and administration of doses for each patient

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

Dispensing of kits for the double-blind treatment period will begin at Visit 2. Trial medication kits will be provided as described in the Flow Chart. 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.

To maintain the blind, all treatments will consist of two tablets of BI 409306 or placebo during the 28 week treatment period, and 1-4 tablets per day during the withdrawal/taper period.

Table 4.1.4: 1 Dosage and treatment schedule for 28 week treatment period

Treatment Group	Dose	Total tablets per daily dose
Placebo	n/a	2 tablets in P.M. (1 25 mg placebo tablet; 1 50mg placebo tablet)
BI 409306	25 mg	2 tablets in P.M. (1 25 mg BI 409306 tablet; 1 50mg placebo tablet)
BI 409306	50 mg	2 tablets in P.M. (1 25 mg placebo tablet; 1 50mg BI 409306 tablet)

Table 4.1.4: 2 Dosage and treatment schedule for 7 day withdrawal/taper period

	Placebo	BI 409306 25 mg **abrupt withdrawal**	BI 409306 25 mg **slow taper**	BI 409306 50 mg **abrupt withdrawal**	BI 409306 50 mg **slow taper**
Day 1 **4 tablets in P.M.**	4 x 10 mg placebo tablets	4 x 10 mg placebo tablets	2 x 10 mg BI 409306 tablets; 2 placebo tablets	4 x 10 mg placebo tablets	4 x 10 mg BI 409306 tablets
Day 2 **3 tablets in P.M.**	3 x 10 mg placebo tablets	3 x 10 mg placebo tablets	2 x 10 mg BI 409306 tablets; 1 placebo tablet	3 x 10 mg placebo tablets	3 x 10 mg BI 409306 tablets
Day 3 **3 tablets in P.M.**	3 x 10 mg placebo tablets	3 x 10 mg placebo tablets	2 x 10 mg BI 409306 tablets; 1 placebo tablet	3 x 10 mg placebo tablets	3 x 10 mg BI 409306 tablets
Day 4 **2 tablets in P.M.**	2 x 10 mg placebo tablets	2 x 10 mg placebo tablets	1 x 10 mg BI 409306 tablet; 1 placebo tablet	2 x 10 mg placebo tablets	2 x 10 mg BI 409306 tablets
Day 5 **2 tablets in P.M.**	2 x 10 mg placebo tablets	2 x 10 mg placebo tablets	1 x 10 mg BI 409306 tablet; 1 placebo tablet	2 x 10 mg placebo tablets	2 x 10 mg BI 409306 tablets
Day 6 **1 tablet in P.M.**	1 x 10 mg placebo tablet	1 x 10 mg placebo tablet	1 x 10 mg BI 409306 tablet	1 x 10 mg placebo tablet	1 x 10 mg BI 409306 tablet
Day 7 **1 tablet in P.M.**	1 x 10 mg placebo tablet	1 x 10 mg placebo tablet	1 x 10 mg BI 409306 tablet	1 x 10 mg placebo tablet	1 x 10 mg BI 409306 tablet

Administration of study drug tablets will be in the evening, preferably just before going to bed. The most common side effects with the use of BI 409306 are visual adverse events occurring at maximum concentration (C_{max}) (30-40 min post-dose). By taking the study drug at bedtime, the negative effect, if any, of experiencing these side effects is expected to be minimized.

Patients should be instructed to take their study medication with water at approximately the same time in the evening, with or without food. BI 409306 tablets should not be chewed or crushed. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled.

A dose reduction of BI 409306 is not possible.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The randomisation code will be kept secret by Clinical Trial Support up to database lock.

See Section 4.1.5.2 for rules of breaking the code for patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

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

Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT. If the code break for a patient is accessed, the sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate CRF page. In case a healthcare professional needs to break the code when the investigator cannot be reached, the code can be opened by calling the 24-hour Emergency helpline located on the trial identification card provided to patients.

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 randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

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 (GMP). 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 local clinical monitor (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 by the IRB / ethics committee ,
- 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 clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- 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, 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 Clinical Trial Protcol (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

Patients should continue to take their current antipsychotic and concomitant psychotropic medications during the treatment period. The dose of these medications should remain unchanged unless necessary for the welfare of the patient. These medications will not be provided as part of the clinical trial supplies.

Any change in dose of concomitant antipsychotic medications should be recorded in the source documentation and on the appropriate pages of the eCRF. Concomitant psychotherapy information should also be recorded in the eCRFs.

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Use of clozapine is not permitted during the study.

Use of medications known to be strong or moderate CYP1A2 inhibitors are not permitted unless it is documented that the patient is NOT a CYP2C19 poor metabolizer. Patients taking medication known to be strong or moderate inhibitors of CYP1A2 must be prospectively genotyped to ensure they are not poor metabolizers of CYP2C19.

A patient who is a CYP2C19 poor metabolizer may discontinue use of a strong or moderate CYP1A2 inhibitor medication prior to randomisation, at the discretion of the Prinicipal Investigator (PI).

Use of strong or moderate CYP1A2 inhibitors taken concomitantly with strong or moderate CYP2C19 inhibitors is not permitted. If a patient needs to take strong or moderate CYP1A2 and CYP2C19 inhibitors during the trial for a short period of time (less than 14 days), study drug should temporarily be discontinued.

A list of strong and moderate CYP1A2 and CYP2C19 inhibitors can be found in the ISF.

Use of St. John's Wort is prohibited. Use of any traditional/herbal/complimentary medication is prohibited during the entire course of study, unless specifically preapproved by the TCM or designee. Any such medication must be stopped during the screening period.

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

4.2.2.2 Restrictions on diet and life style

Because psychoactive drugs may impair thinking, judgment, and/or motor skills, patients will be cautioned about operating machinery, including automobiles, until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities. It is recommended that patients should exercise caution when driving or operating machinery within two hours of drug administration.

Patients should not abuse alcohol or drugs during the study as defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or ICD-10, or in the opinion of the investigator.

There are no other restrictions on diet, exercise, or smoking except that the patient's usual habits, including nicotine and caffeine intake, should not be drastically changed.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

4.3 TREATMENT COMPLIANCE

Study medication will be dispensed to the patient at the study site by designated 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 in the investigator site file.

This trial will employ a medication adherence monitoring platform. The platform uses artificial intelligence on smartphones to confirm study medication ingestion. In addition, built-in reminders and a communication system allows real-time intervention in case of drug interruptions. Use of this platform will in no way supersede or replace the trial prescribed medication protocol of the patients. Because the platform does not change the medication protocol of the patients, but rather encourages adherence to the predefined protocol, use of this platform presents minimal risk to the patients.

The platform monitors each dose of the medication using a smartphone. The platform will be provided to a patient preloaded on a smartphone or the application (app) will be downloaded on the patient's personal smartphone. Patients will receive reminders within predefined time windows to take their medication using the platform. Patients will follow a series of prescribed steps in front of the front-facing smartphone camera to visually confirm ingestion of the medication. The app on the smartphone will make an automated determination of whether the patient has properly taken their medication at the prescribed time. There is no need for site staff to review the administration, or be available at the time the patient is taking their medication. Assistance provided to the patient is automatically reduced as the patient becomes more proficient at using the app.

After local determination by the device of proper medication administration, all video recordings are encrypted and then transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. The captured data and video is reviewable through a roles and rules restricted Health Insurance Portability and Accountability Act (HIPAA) compliant system ensuring privacy of the information. Phone numbers of the patients may also be collected and stored in an encrypted manner, allowing for direct communication to each patient from the system in an automated manner, or by site staff or other study monitoring personnel. At no time is the phone number visible. Individuals outside the clinical sites will not know the identity of the study patients and will have not have access to any medical or health records of the patients.

The platform will allow for rapid and tailored intervention in case of non-adherence (drug interruptions). Site staff will have access to real-time and continuous adherence data without having to rely on self-reported data. Patients who are found to regularly not take their medication will be contacted by site staff for retraining.

Patients must bring all remaining trial medication including empty package material with them when attending visits. Site staff should remind patients of proper drug administration at each visit during the treatment period. Study medication usage and return must be documented on the respective form and an account must be given for any discrepancies.

Treatment compliance will also be calculated based on tablet counts as the number of tablets taken, divided by the number of tablets which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the sponsor.

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

Compliance during the treatment period should be between 80% and 120%. If compliance is outside this range, the patient should be carefully interviewed and re-informed about the purpose and the conduct of the trial. Unreliable patients may be withdrawn from the trial.

The potential for study drug abuse will be closely monitored. Events including overdose, misuse, lost and unaccounted for medication must be thoroughly documented in the patients source and on the appropriate eCRFs.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Relapse will be measured by the batteries and questionnaires listed below, as well as by confirmation of hospitalization, intensive outpatient therapy, or home treatment as an alternative to hospitalization:

Positive and Negative Syndrome Scale (PANSS) will be used to assess the severity of psychotic symptoms and progression of disease. The PANSS positive and negative symptom scales each have 7 items, and the General Psychopathology Scale has 16 items. The patient is rated from 1 to 7 on the 30 different items based on the interview as well as reports from an informant. The total score is the summation of the 30 item scores [R13-5061].

Clinical Global Impressions-Severity (CGI-S) is a one-item evaluation completed by the clinician to measure the severity of psychopathology [R03-0520].

Clinical Global Impressions-Improvement (CGI-I) is a one-item evaluation completed by the clinician to rate total improvement compared to the patient's condition at randomisation.

Patient Global Impressions-Improvement (PGI-I) is a one-item evaluation completed by the patient to assess their overall evaluation of his/her status compared to how they felt at randomisation.

The **Personal and Social Performance scale (PSP)** is a clinician assessment of social functioning in patients with schizophrenia. The PSP measures a patient's functioning in four domains over the past month: (1) socially useful activities, (2) personal and social relationships, (3) self-care and (4) disturbing and aggressive behaviors. A single overall rating score is derived ranging from 1 to 100 with specific criteria for each 10-point interval. Higher scores represent better personal and social functioning [R17-2254].

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

Physical examinations 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, and skin.

Measurement of height and body weight will be performed at the time points specified in the Flow Chart.

The results must be included in the source documents available at the site.

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

5.2.2 Vital signs

Vital signs (systolic/diastolic blood pressure and pulse rate) will be recorded at the study visits as described in the Flow Chart. A similar type of instrument/scale should be used for all measurements. Vital signs will be measured after the patient has been sitting for 5 minutes.

5.2.3 Safety laboratory parameters

Safety laboratory test, which will be assessed at the visits as indicated in the Flow Chart, are listed in Table 5.2.3: 1. Patients should be fasting for at least 8 hours prior to blood collection, except at Visit 1.

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 as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

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 electronic data capture (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.

Table 5.2.3: 1 Safety laboratory tests

Category	Test name
Haematology	Hematocrit Hemoglobin Red Blood Cell (RBC) Count/ Erythrocytes Reticulocyte Count White Blood Cells (WBC) / Leukocytes Platelet Count/ Thrombocytes
	Diff. Automatic (manual if diff. automatic is abnormal) - Neutrophils - Eosinophils - Basophils - Monocytes - Lymphocytes
Coagulation	Partial Thromboplastin Time (=aPTT) Prothrombin time (Quick and INR)

Category	Test name
Chemistry	Aspartate aminotransferase (AST/SGOT) Alanine aminotransferase (ALT/SGPT) Alkaline Phosphatase (AP) Albumin Creatine Kinase (CK) Creatine kinase myocardial b fraction (CK-MB), only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Calcium Sodium Potassium Chloride Bicarbonate Glucose Creatinine Blood urea nitrogen (BUN) Bilirubin Total Bilirubin Direct Bilirubin Indirect Protein, Total Uric Acid Cholesterol, total Triglycerides
Pregnancy test (females only)	Human urine chorionic gonadotropin
Urinalysis (Stix),	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH Urine creatinine
Urine-Sediment (microscopic examination), (only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epith Cells Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Drug screening (urine)	Amphetamines Cannabis Cocaine Methadone Opiates Phencyclidine (PCP)

Category	Test name
Drug assessment in plasma	Refer to lab manual for available antispsychotic assays

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the Flow Chart after 5 minutes in the supine position. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Assessment of Suicidality

Suicidality should be monitored closely during the study period. Suicidal thoughts and behavior will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) (R08-1147). An electronic version utilizing a tablet solution will be used for this trial.

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 C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counselor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the Screening Visit/Visit 1 (using the 'baseline/ screening' version) with the aim to exclude patients with active moderate or severe symptomatology

within a specified time prior to the screening or screening visit. The lifetime history of suicidal ideation and behavior will also be recorded.

After the screening visit, the assessment 'since last visit' version will be performed at each clinic or phone visit. The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the patient, and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the patient'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 behavior, without suicidal intent', standard AE / SAE reporting rules are to be applied.

For each negative report (suicidal ideation type 1, 2 or 3) after the start of the trial, the investigator is to decide based on clinical judgment whether it represents an Adverse Event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly. Refer to Section 5.2.6.1.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient 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.

Serious adverse event

A serious adverse event (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 hospitalisation or
- requires prolongation of existing hospitalisation,
- 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 hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as “deemed serious for any other reason”. AEs which possibly lead to disability will be reported as SAEs.

AEs considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in 5.2.6.2, subsections “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 and/or ALT ≥3 fold ULN (upper limit of normal) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/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" which can be found in the EDC.
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.

5.2.6.2 Adverse event collection and reporting

AE Collection

Patients will be required to report spontaneously any AEs as well as the time of onset, duration and intensity of these events.

If patients report a change in perception or any vision-related AE, site staff must record the patient's verbatim description in the source documents to be reported in the eCRF (and SAE form if applicable). A local ophthalmology assessment will be required if any visual AE is rated as severe by the patient or at the discretion of the Principal Investigator. The ophthalmologist will act as a consultant to the investigator and may offer advice on the proper management and treatment for the reaction.

The potential for study drug abuse-related adverse events will be closely monitored and narratives provided in the Clinical Trial Report (CTR). Narratives will include standard AE data collection, including time of onset, duration, severity and outcome.

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial:
  -all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for AEs but should only report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

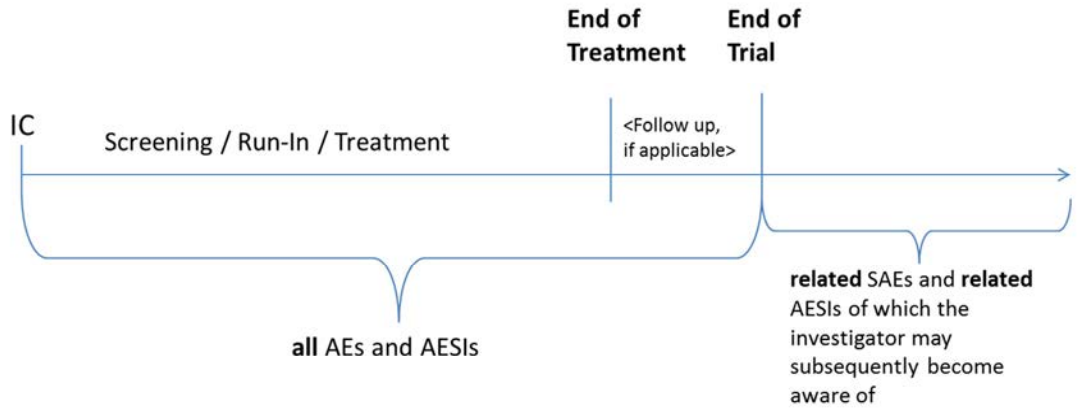


Figure 5.2.6.2: 1 AE Collection

Patients who discontinue trial medication prematurely and agree to be contacted further, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report:

- All AEs/SAEs/AESIs collected by the investigator as instructed in Section 3.3.4.1 for patients who choose Options 1 and 2.
- All AEs/SAEs/AESIs the investigator becomes aware of for patients who choose Options 3 and 4.

After the individual patient's end of the trial the investigator does not need to actively monitor the patient for AEs but should report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

AE reporting to sponsor and timelines

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

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

Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF 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.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of Pharmacokinetics

BI 409306:
Blood samples will be collected as indicated in the Flow Chart to measure plasma concentrations of BI 409306 and metabolites.

From the data collected after first dose, the following individual pharmacokinetic parameters will be reported:
- $C_{0:45h}$: measured plasma concentration of BI 409306 in plasma 0:45 h after single dose of BI 409306.
- $C_{1.5h}$: measured plasma concentration of BI 409306 in plasma 1.5 h after single dose of BI 409306.
- C_{2h}: measured plasma concentration of BI 409306 in plasma 2 h or more after single dose of BI 409306.

From the individual pharmacokinetic parameters $C_{0:45h}$ and $C_{1.5h}$, mean pharmacokinetic parameters will be calculated by descriptive statistics if data allow.

At the post-randomisation visits, the following pharmacokinetic parameters will reported for each analyte:
- C_{press}: residual concentration of BI 409306 and metabolites CD 13896 and CD 14084 in plasma measured after last dose of BI 409306.

See Section 10 for additional information.

5.3.2 Methods of sample collection

5.3.2.1 Plasma sampling for analysis of BI 409306 and metabolites

At Visit 2 blood samples of 3 mL each will be collected from each patient at pre-dose and at 2 post-dose sampling timepoints within the first 1.5 hours after drug intake. One additional blood sample of 3 mL will be collected from each patient at the end of Visit 2 only after all other scheduled procedures have been performed. See Table 10.3:1.

The two metabolites CD 13896 and CD 14084 will be analysed if BI 409306 plasma concentration is BLQ (below the limit of quantification) in the trough samples from Visits 8 and 16, and, if BI 409306 plasma concentrations are above BLQ in two of the samples from Visit 2.

Detailed instructions for obtaining, handling and shipping PK samples are provided in the laboratory manual.

Special attention must be directed to exact timing and instant recording of plasma sampling and drug administration as well as to the correct handling, labelling and storage of samples. At Visit 2, the clock time of the administration of the first BI 409306 dose (during the study visit) and of the actual PK sampling times will be recorded in the eCRF.

At Visits 8 and 16, the clock time of the administration of the last BI 409306 dose (at home) and of the actual PK sampling times will be recorded in the eCRF.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

The relationship between the BI 409306 plasma concentrations and efficacy response and AE may be assessed descriptively.

5.4 ASSESSMENT OF BIOMARKER(S)

5.4.1 Biobanking

Participation in sampling for biobanking (including DNA) is voluntary and not a prerequisite for participation in the trial. A sample for DNA biobanking will be taken only after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Banked samples may be analysed in the future for scientific evaluations or to further, for example, the mechanistic understanding of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions. Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent.
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, including audit trail for clinical data and samples to identify and destroy such samples according to the informed consent form (ICF) is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

5.4.1.1 Methods and Timing of Pharmacogenomic Sample Collection

Sampling will be performed at the time points specified in the Flow Chart. Approximately 8.5 mL of blood will be drawn into a PAXgene Blood DNA tube, preferably at Visit 2. If not feasible at Visit 2, the sample can also be taken at a later visit during the treatment period.

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. DNA, extracted from the original whole blood sample, will be stored at the Sponsor.

5.4.2 Pre-specified Pharmacogenomic Analysis

One blood sample will be taken at the screening visit for genotyping of CYP2C19 from all patients taking medication known to be strong or moderate inhibitors of CYP1A2. Patients classified as poor metabolizers (poor metabolizers defined as presence of two non-functional

alleles (*2 and *3) of the CYP2C19 gene) may be excluded from enrollment (see Section 3.3.3 (Exclusion criteria) and Section 4.2.2.1 (Restrictions regarding concomitant treatment)).

In addition, all randomised patients will be asked for one mandatory blood sample for pre-specified pharmacogenomic analyses at Visit 2. If not feasible at Visit 2, the sample can also be taken at a later visit during the treatment period. In case of a positive study outcome, the sample may be used for DNA extraction and subsequent genotyping for variants in genes involved in absorption, distribution, metabolism and elimination of the compound. It is not intended to include these data in the final report. However, the data may be part of the report if necessary.

All remaining samples will be destroyed no later than two years after the end of the trial.

Detailed instructions on sampling, preparation, processing, shipment and storage of the samples are provided in the laboratory manual.

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are acceptable measurements and commonly used in monitoring safety aspects or assessing treatment response in patients meeting diagnostic criteria for schizophrenia.

The scheduled measurements are appropriate to see drug induced changes in physical examination, vital signs, ECG and standard laboratory values. The primary and secondary efficacy endpoints and safety endpoints are standard and accepted for evaluation of safety and tolerability of an oral drug.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. If any visit needs to be rescheduled, subsequent visits should follow the original visit date schedule by referring to the date of randomisation (Visit 2).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart. Additional details regarding visit procedures are provided in Section 5 and below.

The members of the site staff that will be administering the assessments have to be properly trained (either at the investigator meeting or individually), and training documentation must be filed 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 assessments.

6.2.1 Screening Period

No trial procedures should begin until the patient has signed the informed consent. After a patient has signed the informed consent, the patient is enrolled in the trial and has begun screening. The patient should be recorded on the enrolment log and be registered in the IRT as a screened patient. The Screening procedures are not required to be completed on the same day.

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

Patients who have a laboratory test value outside the range that would jeopardize patients' safety while participating in this clinical trial may have the test repeated once to determine eligibility; however, the result must be available prior to Visit 2 (Day 1). The site should inform the authorized monitors (CML/Clinical Research Associate (CRA)) of their intent to redraw a sample(s) and receive the approval from the CML before they send out the retest sample to the central laboratory.

Patients who are not eligible for randomisation should be entered as a screen failure in IRT.

Patients who failed screening may repeat the screening phase once after discussion between the investigator and sponsor, providing the reasons for screening failure were reversible and have been resolved. Permission to rescreen patients must be obtained from the TCM or CML, and documentation of approval filed in the ISF. The patient who will be rescreened needs to be re-consented and be given a new patient number. All the study procedures for the Screening Visit (Visit 1) must be repeated upon rescreen.

6.2.2 Treatment period(s)

Eligible patients will be trained and set-up with the smartphone medication adherence monitoring Platform at Visit 2 prior to taking their first dose of study drug. Please refer to the manual in the ISF.

Study medication will be allocated via IRT and dispensed at visits specified in the Flow Chart. Patients will be assigned a new medication number(s) at each of these visits. The first dose of study drug will be administered at the site after all baseline assessments have been completed and trial eligibility confirmed at Visit 2.

See Sections 5.3.2 and Section 10.3 for the sampling methods and time schedule for PK blood sampling.

Phone Visits are to be conducted at the time points specified in the Flow Chart to assess the overall status of the patient, assess suicidality, check compliance, and to collect new AE and concomitant medication information. If symptom worsening is suspected, an unscheduled in-clinic visit should be scheduled to further assess the patient for relapse. During the unscheduled visit, information should be gathered to determine whether any criteria for relapse have been met. PANSS and CGI-S should be assessed, as well as any other assessments necessary to assess the patient's condition, in the judgment of the investigator.

Relapse of Schizophrenia

If the criteria for relapse (See Section 2.1.2) have been met, additional treatment considered necessary for the patient's welfare may be given. The patient may continue in the trial at the discretion of the investigator.

A blood sample should be collected at the time relapse is diagnosed to measure for detectable levels of antipsychotic medication.

Patients prematurely discontinuing study drug:

Patients who discontinue study drug prematurely should ideally be observed until study end as if they were still receiving blinded study treatment. There are 4 Options for observing patients after premature drug discontinuation. See Section 3.3.4.1

Early D/C Option 1: For patients who prematurely discontinue taking study drug who are willing to conduct the remaining visits, the following should be performed:

- EOT Visit must be performed within 7 days of last intake of study drug, or as soon as possible.
- Thereafter, patients should be followed up according to the regular visit schedule through Visit 16.
- A Follow-Up Visit is not necessary if the patient discontinued >4 weeks prior to Visit 16. If a patient discontinues <4 weeks prior to Visit 16, a Follow-up Visit will be performed 28 days after the EOT Visit.

Early D/C Option 2: For patients who prematurely discontinue taking study drug who are willing to conduct the remaining visits over the phone, the following should be performed:

- EOT Visit must be performed within 7 days of last intake of study drug, or as soon as possible.
- A Follow-up Visit will be performed 28 days after the EOT Visit.
- Thereafter, patients should be followed up over the phone according to the regular visit schedule through Visit 16. See Section 3.3.4.1 for Early D/C Option 2 which details the assessments to be conducted via phone.

Early D/C Options 3 and 4: For patients who prematurely discontinue study drug and agree to be contacted or have information collected from an alternative source at the end of the study, the following should be performed:

- EOT Visit must be performed within 7 days of last intake of study drug, or as soon as possible.
- A Follow-up visit will be performed 28 days after the EOT Visit.
- Occurrence of psychiatric illness/relapse and vital status must be collected approximately 28 weeks after the patient was randomised.

6.2.2.1 Withdrawal/Taper Period

Patients who complete the 28 week treatment period will enter the withdrawal/taper period. When patients are randomised at Visit 2, they are also randomised to either abrupt withdrawal or slow taper of study drug. Vital signs, suicidality and adverse events will be closely monitored during this period.

Refer to Section 7.3.4 for the withdrawal/taper analysis strategy.

6.2.3 Follow up period and trial completion

Patients who complete the treatment and withdrawal/taper periods will have a Follow-Up Visit performed at Week 32. Patients who enter the withdrawal/taper period, but discontinue taking their study drug will have a Follow-up Visit as planned at Week 32.

For patients who prematurely discontinue taking study drug who are willing to conduct the remaining in-clinic and phone visits (Early D/C Option 1), a Follow-Up Visit is not necessary if the patient discontinued >4 weeks prior to Visit 16. If a patient discontinues <4 weeks prior to Visit 16, a Follow-up Visit should be performed 28 days after the EOT Visit.

A Follow-Up Visit will be performed 28 days after the EOT Visit for patients who prematurely discontinue taking study drug and agree to conduct the remaining visits over the phone or who agree to be contacted or have information collected from an alternative source at the end of the study (Early D/C Options 2-4).

Occurrence of AEs since last visit will be documented and will be managed in accordance with Section 5.2.6. All AEs and/or SAEs persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, double-blind, parallel group, multi-centre trial aiming to show superiority of BI 409306 to placebo as an intervention to prevent relapse in patients with schizophrenia. All patients will be treated for 28 weeks.

The primary objective of the statistical analysis is to determine whether BI 409306 significantly reduces the risk of relapse in comparison to placebo.

The estimand of primary efficacy interest is the test of the hazard ratio of BI 409306 (25 mg q.d. and 50 mg q.d. pooled) vs. placebo using the Wald test for the treatment effect in a stratified Cox proportional hazards model stratified by country, on the full analysis set using the ITT follow-up analysis period. Refer to Sections 7.2 and 7.3 for more details.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The trial will follow a hierarchical testing strategy. The first hypothesis for the superiority testing of the primary endpoint time to first relapse is (HR = hazard ratio):

> H_o: $HR_{BI\ 409306\ /\ placebo} = 1$ vs. H_a: $HR_{BI\ 409306\ /\ placebo} \neq 1$, where $HR_{BI\ 409306}$ is the hazard ratio for the pooled active treatment arms (i.e. BI 409306 50 mg q.d. and BI 409306 25 mg q.d.), over 28 weeks (excluding the withdrawal/taper period)

Superiority will be declared if the hazard ratio between BI 409306 vs. placebo is statistically significantly less than 1 at the two-sided type I error level $\alpha = 0.05$.

If the first hypothesis test is determined to be statistically significant, the individual doses will be tested for superiority using Hochberg's step-up test. The method will be to perform the statistical tests and rank the p-values for the individual doses vs. placebo. Let $p_{(1)} \geq p_{(2)}$ be the two-sided p-values. The corresponding null hypotheses are $H_{0(1)}$ and $H_{0(2)}$.

> $H_{0(1)}$: $HR_{BI\ 409306\ /\ placebo} = 1$ vs. $H_{a(1)}$: $HR_{BI\ 409306\ /\ placebo} \neq 1$, where $HR_{BI\ 409306}$ is the hazard ratio for the BI 409306 dose with the highest p-value

> $H_{0(2)}$: $HR_{BI\ 409306\ /\ placebo} = 1$ vs. $H_{a(2)}$: $HR_{BI\ 409306\ /\ placebo} \neq 1$, where $HR_{BI\ 409306}$ is the hazard ratio for the BI 409306 dose with the lowest p-value

Step 1: If $p_{(1)} \leq 0.05$ then both hypotheses are rejected and both doses are declared statistically significant and testing ends. If $p_{(1)} > 0.05$, then $H_{0\ (1)}$ is not rejected and the testing proceeds to Step 2.

Step 2: If $p_{(2)} \leq 0.025$, then $H_{0\ (2)}$ is rejected and this dose is declared statistically significant. If $p_{(2)} > 0.025$, then all doses fail.

The remaining alpha after the testing of the primary endpoint (Steps 1 and 2) will be used to test the key secondary endpoint of change from baseline in PANSS positive symptoms. The hypotheses to be tested are:

$H_{0(3)}$: Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with BI 409306
≥ Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with placebo

$H_{a(3)}$: Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with BI 409306
< Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with placebo

The first of the key secondary hypothesis to be tested will be based on the pooled active treatment arms (i.e. BI 409306 50 mg q.d. and BI 409306 25 mg q.d.), over 28 weeks (excluding the withdrawal/taper period).

Similar to the primary endpoint, if the first hypothesis test (on the pooled doses) is determined to be statistically significant, the individual doses will be tested for superiority using Hochberg's step-up test as described above.

7.3 PLANNED ANALYSES

Two patient populations are defined:

- The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment
- The full analysis set (FAS) includes all patients in the treated set with at least one post-baseline measurement of any type

No per protocol population will be used for analyses; however protocol violations will be identified and listed.

Analysis sets will be fully defined in TSAP.

Three analysis periods are defined:

- **Intent to Treat (ITT) follow-up:** from treatment start date until the end of the intended complete treatment period:

  For patients who complete the trial according to the flow chart, the withdrawal/taper period is not included. Additionally, if a patient happens to take drug for 29 weeks (i.e. 1 week longer than the planned 28 weeks) and then begin the withdrawal/taper period, the withdrawal/taper period will not be included.

For patients who discontinue prior to the 28 week treatment period, e.g. at week 25, the follow-up period until the end of week 28, is included.

- **Full follow-up:** from randomisation until the end of the trial, including all observed time on and off trial medication until the follow-up visit or the last date of contact:

  For patients who discontinue trial medication according to the flow chart, the withdrawal/taper period is included. Additionally, if a patient happens to take drug for 29 weeks (i.e. 1 week longer than the planned 28 weeks) and then begin the withdrawal/taper period, the withdrawal/taper period is included.

  For patients who discontinue prior to the 28 week treatment period, e.g. at week 25, the follow-up period until the last contact date is included.

  The full follow-up analysis period will be used as a sensitivity analysis to the ITT follow-up analysis.

- **On-treatment:** from treatment start date until the date of discontinuation of trial medication + 7 days:

  For all patients this analysis period includes only the time on trial medication + 7 days after taken off trial medication.

  For patients randomised to the withdrawal period, this will include 28 weeks of treatment, or for early discontinued patients, the time period on active treatment prior to discontinuation + 7 days, which corresponds to the 7 days abrupt withdrawal period.
  For patients randomised to the taper period, this will include 28 weeks of treatment + the tapering period (of 7 days) + 7 days, or for early discontinued patients, simply the time period on randomised active treatment prior to discontinuation + 7 days (because tapering will not be done for patients discontinued early).

  The on-treatment analysis period will be used to analyse safety.

7.3.1 Primary endpoint analyses

The primary endpoint is the time to first relapse as defined in Section 2.1.2 over the ITT follow-up period (see definition in Section 7.3).

The treatment comparison strategy is specified in Section 7.2. The treatment arms will be pooled according to dose, i.e. no distinction will be made between treatment arm randomised to taper or treatment arm randomised to withdrawal.

The equality of the hazard rates will be tested by the Wald test for the treatment effect in a stratified Cox proportional hazards model at the two-sided 5% significance level. The model includes the treatment effect as the only covariate and is stratified by country. Breslow's method for handling ties will be used.

The same stratified Cox proportional hazards model will be used to estimate the hazard ratio of BI 409306 vs. placebo and the asymptotic 95% Wald confidence interval. A hazard ratio of less than one favors BI 409306. The analysis will be implemented using SAS® PROC PHREG. Cox proportional hazard model assumptions will be verified.

In early discontinued patients, if the occurance of a relapse cannot be determined between the time of discontinuation and last contact, it is assumed that no relapse has occurred.
Patients who discontinue study medication will be followed until the end of the trial for the primary endpoint. Patients who are lost-to-follow up will be censored for the primary endpoint at the date of last known patient contact.

A sensitivity analysis will be conducted on the primary endpoint, using the Full Follow-up period (see definition above).

7.3.2 Secondary endpoint analyses

Key secondary analysis
The key secondary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline of PANSS positive symptoms score after 28 weeks of treatment (Section 7.2).
The analysis will include the fixed, categorical effects of treatment at each visit, and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
The statistical model will be as follows:

$$y_{ijkm}=\beta_j S_i + \tau_{jk} + \phi_m + e_{ij}$$
$$e_{ij} \sim N_Z\,(\boldsymbol{0, \Sigma})$$

y_{ijkm} = response variable for subject i in country m at visit j receiving treatment k
S_i = the baseline measurement of subject i, i=1,2,…
β_j = coefficient of baseline effect at visit j
τ_{jk} = the effect of treatment k at visit j, j=1,…,Z and k=1,…,Y
ϕ_m = the effect of country m, m=1,…,X
e_{ij} = the random error associated with the j^{th} visit of the i^{th} subject. Errors are independent between subjects.
$\boldsymbol{\Sigma}$ = an unstructured covariance matrix.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ or the remaining alpha (two-sided ((1- α)% confidence intervals).The treatment comparison will be the contrast between treatments at the endpoint visit.

The key secondary analysis will be performed on the FAS. Patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance.

Procedures to follow if the analysis fails to converge will be described in the TSAP.

To assess the homogeneity of the treatment effect on the primary endpoint across the levels of the country stratification, the same MMRM model will be fitted but replacing the treatment-by-visit term by a treatment-by-country-by-visit term. A descriptive p-value of treatment effect homogeneity at 28 weeks will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.

Secondary analysis

Time to change in antipshychotic medication will be analysed in the same manner as the primary endpoint using the stratified Cox proportional hazards model.

Additionally, the analyses for suicidal ideation and behaviour as assessed by C-SSRS will be analysed by calculating a relative risk reduction and providing a 95% confidence interval around the RRR.

The PGI-I score, change in CGI-S and PSP will be summarized descriptively.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period (see above) 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 adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the

residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of 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, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Withdrawal/taper period

As described in Section 3.1, during the initial randomisation phase, patients will be randomised to either BI 409306 50 mg qd and either abrupt withdrawal or slow taper, or BI 409306 25 mg qd and either abrupt withdrawal or slow taper, or Placebo. This 7-day, post 28-week treatment, withdrawal/taper period will assess the impact of abrupt withdrawal versus slow taper of study drug to assess drug dependency, and does not affect the primary 28-week analysis, for which the doses will be pooled and the assignment to taper vs. withdrawal during randomisation will not be taken into account.

Contrary to the primary analysis, in which the randomisation to a withdrawal/taper group will be ignored, this safety analysis will assess the following:

- Change in vital signs
- Change in suicidality
- Adverse events

The analyses will be descriptive only and will be performed only on patients who were randomised to an active treatment arm and will include three different comparisons, which will analysed hierarchically:

1. the effect of tapering versus abrupt withdrawal when both doses are pooled.

If an effect is apparent, then the next evaluation will be:

2. the effect of dose dependency

and finally,

3. the interaction between dose dependency and the withdrawal/taper.

All these analyses will only use the data obtained during the withdrawal/taper period.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

The relationship between the BI 409306 plasma concentrations and efficacy response and AE may be assessed descriptively.

In case the primary analysis demonstrates a drug effect, PK analysis on all plasma concentrations will be performed by population PK and PK/PD modelling (i.e. exposure-response). These pharmacometric analyses, if performed, will be reported separately.

7.4 INTERIM ANALYSES

No interim analysis is planned but blinded evaluation of the relapse rate will be conducted on an ongoing basis and blinded sample size re-calculations may be performed.

7.5 HANDLING OF MISSING DATA

All patients will be followed up for relapse to the greatest possible extent as described in Section 3.3.4.1. Any patient who has not relapsed will be censored in the analysis of the primary endpoint at the time of last patient contact. For any secondary analysis using RRR, all patients in the FAS will be included in the calculation of the RRR, regardless of dropout.

For the key secondary analyses, if a patient misses a visit, the data will not be imputed. The mixed effects model will handle missing data based on a likelihood method under the "missing at random" assumption.

Further details about handling missing data will be specified in the TSAP.

7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment equally to three treatment arms (25 mg q.d. BI 409306, 50 mg q.d. BI 409306 or placebo). Additionally, patients will be randomised equally to a one-week taper or withdrawal period immediately after the 28 week treatment discontination. The randomisations will occur together using the IRT in a 1:1:1:1:1:1 ratio. The randomisation will be stratified by country.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

Sample size considerations are given in Table 7.7: 1 based on background placebo relapse rates of 25% and 30% and for hazard redeductions for the combined BI 409306 groups vs.

placebo ranging from 45% to 55%, 80% power, a two-sided alpha = 0.05, and 20% dropout after six months.

Table 7.7: 1 Trial sample sizes for selected assumptions of hazard ratios and proportions of placebo failures, with 20% dropout, 80% power, and α=0.05

	Hazard reduction[a] for BI 409306 (both groups combined) to placebo		
Placebo failure rate	55%[a]	50%[a]	45%[a]
30%	305	385	494
25%	372	470	603

[a] 55% hazard reduction is the same as a hazard ratio of 0.45; 45% hazard reduction is the same as a hazard ratio of 0.55

The sample size selected was 385 under the assumption that the relapse rate for placebo is 30% and the hazard reduction for BI 409306 is 50%. One hundred twenty-nine (129) patients will be randomised per treatment group in a 1:1:1, making the target total number of randomised patients to be 387.

Seventy-four (74) events (relapses) are needed to be observed to meet the trial objective of 80% power for the comparison of BI 409306 (N=258 for 25 mg q.d. and 50 mg q.d. combined) to placebo (N=129). This will not be an event driven trial, so the trial will end when all randomised patients have reached 6 months exposure, regardless of number of conversions observed.

Calculations were performed using ADDPLAN® 6.1.1 statistical package by [redacted].

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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 Clinical Trial Report. The certificate of insurance coverage is made available to the investigator and the patients, and is stored in the ISF.

8.1 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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents.

For Japan only: The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

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 good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF 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 call with the treating physician cannot be conducted, the TCM or CML should be contacted for further discussion.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see Section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly

been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The 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 CRF 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. FDA). They may review all CRFs 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 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 (WHO) GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

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 Treat"** date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after "**Last Patient Last Treat"** at their site.

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

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

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

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

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

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. Investigators will be selected to participate who have experience with conducting trials in patients with schizophrenia.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the (Investigator Site File) ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

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

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,

- ensure appropriate training and information of Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operative 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 service provider has been selected to provide a tablet-based solution for select instruments and scales for patient assessment. This vendor will also support tasks related to rater prequalification, rater training, provision of rater materials, and central review of PANSS assessments for quality. These responsibilities and tasks will be defined in a written contract before initiation of the clinical trial.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF. In addition, a vendor will be used to to monitor medication adherence using a smartphone application.

9. REFERENCES

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10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

For pharmacokinetic analysis and displays, concentrations will be used in the same format as reported in the bioanalytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the reporting of pharmacokinetic parameters. Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables.

For the presentation of the mean profiles, the arithmetic and geometric mean and the planned blood sampling times will be used.

10.1.1 Handling of missing data

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

10.2 HANDLING PROCEDURE OF BLOOD SAMPLES FOR PLASMA CONCENTRATION-TIME MEASUREMENTS

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

Refer to the lab manual for detailed instructions for obtaining, handling and shipping PK samples.

10.3 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Table 10.3: 1 Time schedule for PK blood sampling (BI 409306)

Visit	Day	Time Point [hh:min]	CRF Time /PTM[1]	Event	Sample No.
2	1	Just before drug administration	-0:05	PK Blood	1
		0:00	0:00	Drug administr.	---
		0:45 minutes (15 minutes – 1:00 h)	0:45	PK Blood	2
		1:30 (1:00 to 2:00 h)	1:30	PK Blood	3*
		End of study procedures/visit (After 2 hour post dose. No upper time window applied)	2:00	PK Blood	4*
8	85	8:00-24:00	8:00-24:00	PK Blood	5
16	197	8:00-24:00	8:00-24:00	PK Blood	6

1. Planned time

*Due to wide sampling window, the 3nd and 4rd samples must be at least 30 minutes from the previous collected sample (i.e. all PK samples are to be collected within their respective sampling window, plus they will be at least 30 minutes apart from each other).

The two metabolites CD 13896 and CD 14084 will be analysed if BI 409306 plasma concentration is BLQ in the through samples from Visits 8 and 16, and, if BI 409306 plasma concentrations are above BLQ in two of the samples from Visit 2.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		08 Nov 2017
EudraCT number		2017-002369-23
BI Trial number		1289-0049
BI Investigational Product(s)		BI 409306
Title of protocol		A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 28-week treatment period as adjunctive therapy to antipsychotic treatment for the prevention of relapse in patients with schizophrenia.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Synopsis
Description of change		**Secondary efficacy endpoints:** Key secondary endpoint: • Change from baseline in Positive and Negative Symptom Score (PANSS) positive symptoms score after 28 weeks of treatment. Secondary endpoints: • Time to new prescription or increase in dose of an ongoing antipsychotic medication. • Change from baseline in Clinical Global Impressions–Severity (CGI-S) scale score after 28 weeks of treatment. • Patient Global Impressions-Improvement (PGI-I) scale score after 28 weeks of

		treatment. • Suicidal ideation and behaviour as assessed by C-SSRS after 28 weeks of treatment. • Change from baseline in Personal and Social Performance scale (PSP) score after 28 weeks of treatment.
Rationale for change		Key secondary endpoint added
Section to be changed		2.1.3 Secondary Endpoints
Description of change		**Secondary efficacy endpoints:** Key secondary endpoint: • Change from baseline in Positive and Negative Symptom Score (PANSS) positive symptoms score after 28 weeks of treatment. Secondary endpoints: • Time to new prescription or increase in dose of an ongoing antipsychotic medication. • Change from baseline in Clinical Global Impressions–Severity (CGI-S) scale score after 28 weeks of treatment. • Patient Global Impressions-Improvement (PGI-I) scale score after 28 weeks of treatment. • Suicidal ideation and behaviour as assessed by C-SSRS after 28 weeks of treatment. Change from baseline in Personal and Social Performance scale (PSP) score after 28 weeks of treatment.
Rationale for change		Key secondary endpoint added
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		3.3.2 Inclusion criteria
Description of change		3. Patients currently taking a stable dose of antipsychotic medication(s) for at least ~~8~~ 12 weeks

		prior to randomisation. 4. Detectable level of current antipsychotic medication(s) in plasma ~~or serum~~ from blood drawn at Visit 1 (unless no assay is available for the antipsychotic(s) currently prescribed). 6. CGI-S score ≤4 at Visits 1 and 2. 7. PANSS total score ≤80 and a score of ≤ 4 on ~~all~~ individual PANSS items conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content at Visit 1.
Rationale for change		#3 and #6: To ensure clinical stability of patients entering the study. #4: Updated to reflect that the lab will analyse plasma. #7: Clarification that the four items listed in this criterion must be ≤ 4.
Section to be changed		7.2 NULL AND ALTERNATIVE HYPOTHESES
Description of change		Step 1: If $p_{(1)} \leq 0.05$ then both hypotheses are rejected and both doses are declared statistically significant and testing ends. If $p_{(1)} > 0.05$, then $H_{0(1)}$ ~~is accepted~~ not rejected and the testing proceeds to Step 2. Step 2: If $p_{(2)} \leq 0.025$, then $H_{0(2)}$ is rejected and this dose is declared statistically significant. If $p_{(2)} > 0.025$, then all doses fail. The remaining alpha after the testing of the primary endpoint (Steps 1 and 2) will be used to test the key secondary endpoint of change from baseline in PANSS positive symptoms. The hypotheses to be tested are: $H_{0(3)}$: Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with BI 409306 ≥ Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with placebo $H_{a(3)}$: Mean change from baseline of PANSS

		positive symptom score after 28 weeks of treatment with BI 409306 < Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with placebo The first of the key secondary hypothesis to be tested will be based on the pooled active treatment arms (i.e. BI 409306 50 mg q.d. and BI 409306 25 mg q.d.), over 28 weeks (excluding the withdrawal/taper period). Similar to the primary endpoint, if the first hypothesis test (on the pooled doses) is determined to be statistically significant, the individual doses will be tested for superiority using Hochberg's step-up test as described above.
Rationale for change		Key secondary endpoint added
Section to be changed		7.3.2 Secondary endpoint analyses
Description of change		Key secondary analysis The key secondary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline of PANSS positive symptoms score after 28 weeks of treatment (Section 7.2). The analysis will include the fixed, categorical effects of treatment at each visit, and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The statistical model will be as follows: $y_{ijkm}=\beta_j S_i + \tau_{jk} + \phi_m + e_{ij}$ $e_{ij} \sim N_Z(\mathbf{0}, \boldsymbol{\Sigma})$. y_{ijkm} = response variable for subject i in country m at visit j receiving treatment k S_i = the baseline measurement of subject i, i=1,2,… β_j = coefficient of baseline effect at visit j τ_{jk} = the effect of treatment k at visit j, j=1,…,Z and k=1,…,Y ϕ_m = the effect of country m, m=1,…,X e_{ij} = the random error associated with the j^{th}

		visit of the i^{th} subject. Errors are independent between subjects. Σ = an unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α = 0.05 or the remaining alpha (two-sided ((1- α)% confidence intervals).The treatment comparison will be the contrast between treatments at the endpoint visit. The key secondary analysis will be performed on the FAS. Patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance. Procedures to follow if the analysis fails to converge will be described in the TSAP. To assess the homogeneity of the treatment effect on the primary endpoint across the levels of the country stratification, the same MMRM model will be fitted but replacing the treatment-by-visit term by a treatment-by-country-by-visit term. A descriptive p-value of treatment effect homogeneity at 28 weeks will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable. Secondary analysis
Rationale for change		Key secondary endpoint added
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		7.5 HANDLING OF MISSING DATA
Description of change		For the key secondary analyses, if a patient misses

		a visit, the data will not be imputed. The mixed effects model will handle missing data based on a likelihood method under the "missing at random" assumption.
Rationale for change		Key secondary endpoint added
Section to be changed		8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT
Description of change		For Japan only: The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent. These two sentences are only applicable in Japan.
Rationale for change		These two sentences are only applicable in Japan.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

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