Clinical Trial Protocol

	Document Number:	**c08964447-05**
EudraCT No.: **EU Trial No:**	2016-004973-42	
BI Trial No.:	1289-0032	
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 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.	
Lay Title:	This study tests whether BI 409306 prevents patients with a specific type of mental illness (attenuated psychosis syndrome) from becoming worse. This study looks at how well patients tolerate the medicine and how effective it is over 1 year.	
Clinical Phase:	II	
Trial Clinical Monitor:	[redacted] Phone: Email:	
Coordinating Investigator:	[redacted] Phone: Email:	
Status:	Final Protocol (Revised Protocol based on global amendment 3)	
Version and Date:	**Version: 4.0**	**Date: 04 Oct 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 409306	
Protocol date: 09 Mar 2017	**Trial number:** 1289-0032		**Revision date:** 04 Oct 2018

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 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.
Coordinating Investigator:	[redacted]
Trial site(s):	Multicentre trial
Clinical phase:	II
Objective(s):	To investigate the efficacy, safety and tolerability of BI 409306 compared to placebo given for 52 weeks to patients with attenuated psychosis syndrome. The study is designed to show superiority of BI 409306 over placebo in achieving remission of APS, as well as improvement in cognition and functional capacity.
Methodology:	Multinational, multicentre, randomised, double-blind, placebo-controlled, parallel group study
No. of patients:	
total entered:	300
each treatment:	150 per treatment group
Diagnosis :	Patients meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for Attenuated

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	Psychosis Syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS).
Main criteria for inclusion:	Patients who are ≥16 and ≤ 30 years old who meet diagnostic criteria for Attenuated Psychosis Syndrome (APS) per DSM-5 as determined by the Structured Interview for Psychosis-Risk Syndromes (SIPS).
Test product(s):	BI 409306
dose:	50 mg b.i.d.(twice daily dosing)
mode of administration:	p.o. (oral)
Comparator products:	Matching placebo
dose:	Not applicable
mode of administration:	p.o.
Duration of treatment:	52 weeks
Endpoints	Primary endpoint: The primary endpoint is time to remission from APS within a 52 week timeframe. Remission from APS is defined as a score of <3 on all of the P1-P5 Positive Symptom items of the SOPS and maintained until the end of treatment. Secondary endpoints: • Time to first episode of psychosis within a 52 week timeframe

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	as adjudicated by the Central Rating Committee. First episode of psychosis defined as one or more SOPS P1-P5 rated a 6 AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month. OR a new prescription or increase in dose of an ongoing antipsychotic medication. Time of onset of first episode psychosis is defined using the rater's best estimate as determined in the SOPS interview or when the patient began taking a new prescription or increased the dose of antipsychotic medication. • Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 24 and 52 weeks of treatment. • Change from baseline in the Tablet based Brief Assessment of Cognition (BAC App) composite T score after 52 weeks of treatment. • Change from baseline in Positive and Negative Syndrome Scale (PANSS) positive items score, negative items score, and total score after 52 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 remission from APS, 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 10% significance level. The model includes the treatment effect and

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	categorized NAPLS risk score as covariates and is stratified by baseline use of antipsychotics. Time to event endpoints will be analysed using Cox proportional hazard model and change from baseline endpoints will be analysed using the restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM).		

FLOW CHART

Trial Periods	Screening Period	Randomized Treatment Period																						Completed Patients	Early D/C Option 1	Early D/C Options 2-4	Follow-up Period	
Visit	**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**EOT****	**EOT****	**EOT****	**F/U*****	**End of Study******
Study week	**-4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**52**	**52**			**56**	
Study day	**-28**	1	8	15	22	29	36	43	64	85	106	127	148	169	190	211	232	253	274	295	316	337	365	365			393	
Visit window in days	-28 to -7	N/A	+/- 1	+/- 2	+/- 1	+/- 2	+/- 1	+/- 2	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3			+/- 3	
Informed consent[1]	X																											
Demographics	X																											
Medical history	X																											
Physical examination	X									X				X				X					X			X		
Vital signs	X	X		X		X		X		X		X		X		X		X		X		X	X		X	X	X	
Height	X													X									X			X		
Weight	X	X								X				X				X					X		X	X	X	
Pregnancy test (urine; females only) [2]	X	X		X		X		X		X		X		X		X		X		X		X	X			X		
12 lead-ECG[3]	X							X		X		X		X		X		X		X		X	X			X		
Safety laboratory tests (urine/blood)[4]	X	X						X		X		X		X		X		X		X		X	X		X	X	X	
Substance Use Assessment[5]	X																											
Urine drug screen	X	X								X				X				X					X			X		
Salivary Cortisol[6]		X								X				X									X			X		
BDNF, Inflammatory Cytokines Sampling[6]		X								X				X									X			X		
Pharmacogenomic sampling	X[7]	X[8]																										
Optional DNA biobanking (requires separate ICF)[9]		X																										
SIPS[10]	X																						X			X		
SOPS[10]		X		X		X		X		X		X		X		X		X		X		X			X		X	
Global Functioning: Social	X									X				X				X					X			X		
BACS-SC & HVLT-R[11]	X									X				X				X					X			X		
BAC App[12]		X										X				X							X			X		
Phone Visit[13]			X		X		X		X		X		X		X		X		X		X							

FLOW CHART (cont.)

Trial Periods	Screening Period	Randomized Treatment Period																						Completed Patients	Early D/C Option 1	Early D/C Options 2-4	Follow-up Period	
Visit	**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**EOT****	**EOT****	**EOT****	**F/U*****	**End of Study******
Study week	**-4**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**	**52**	**52**			**56**	
Study day	**-28**	1	8	15	22	29	36	43	64	85	106	127	148	169	190	211	232	253	274	295	316	337	365	365			393	
Visit window in days	-28 to -7	N/A	+/- 1	+/- 2	+/- 1	+/- 2	+/- 1	+/- 2	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3			+/- 3	
eC-SSRS[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
[redacted]		X						X		X		X		X		X		X		X		X	X			X		
PANSS[15]		X												X									X			X		
[redacted]	X																						X			X		
In-/Exclusion Criteria	X	X[16]																										
Randomization (via IRT)		X[17]																										
SCoRS[18]		X								X				X				X					X			X		
[redacted]		X		X				X		X				X				X					X		X	X	X	
[redacted]		X										X								X			X			X		
[redacted]		X								X				X				X					X			X		
[redacted]										X				X				X					X			X		
[redacted]										X				X				X					X			X		
Brief Supportive Psychoeducation		X		X		X																	X			X		
[redacted]		X																					X			X		
Interactive Response Technology Use[19]	X	X						X		X		X		X		X		X		X		X	X		X	X		
Dispense study drug		X						X		X		X		X		X		X		X		X						
Smartphone app training, set-up/ In-clinic drug administration		X																										
Adverse events/Outcome Events[20]	X	X	X	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		X	X	X	
Compliance check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		
Termination of trial med.																								X	X	X		
Trial Completion																												X
NAPLS Risk Calculator[21]	X																						X			X		
Vital Status																												X[22]

* Screening Visit procedures are not required to be completed on the same day.

** EOT for patients who complete the treatment period should be completed at Visit 23. 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 6.2.3 provide additional information.
Early 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 for both in-clinic and phone visits. Visit 23 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 one year after the patient was randomized.

*** Patients who complete the treatment period will be scheduled for a Follow-Up Visit 28 days after Visit 23. Patients who prematurely discontinue study medication and choose Early D/C Option 1 will not need a Follow-Up Visit. Patients who prematurely discontinue study medication and choose Early D/C Options 2-4 will be scheduled for a Follow-Up Visit 28 days after the EOT visit. See Sections 3.3.4.1, 6.2.2, and 6.2.3.

**** The End of Study CRFs will be completed at the time of the Follow-Up Visit for completed patients. Patients who prematurely discontinue study drug and remain in the study will have the End of Study CRFs completed one year after randomization.

1 Written informed consents/assents 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). Patients who sign the assent and reach the age of majority during the trial must sign the current version of the informed consent. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's and IRB/IEC's instructions.

2 Female patients of childbearing potential must perform urine (dipstick) pregnancy test at in-clinic Visits 1 through Visit 23/EOT.

3 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/assent for main study has been obtained.

4 Routine laboratory tests are hematology, chemistry, coagulation, urinalysis, and endocrine parameters as described in Table 5.3.3:1. Patients should be fasting for at least 8 hours prior to the blood samples collected at Visit 2 and Visit 23/EOT.

5 Patients will be asked whether they have ever or are currently using/consuming tobacco, alcohol and cannabis.

6 Saliva and blood samples should be collected at approximately the same time of the day at each visit. Baseline samples must be collected prior to first dose. Patients will be instructed to refrain from caffeine, alcohol, dairy products, and nonprescription medications the evening before and the morning of saliva sampling.

7 One blood sample will be taken at screening for genotyping of CYP2C19 from all patients taking medication known to be strong or moderate inhibitors of CYP1A2.

8 One blood sample for the analysis of pre-specified genes will be collected at Visit 2 from all patients.

9 Collection of a sample for DNA biobanking is optional (See Section 5.5 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.

10 The Structured Interview for Psychosis-Risk Syndromes (SIPS) and Scale of Prodromal Symptoms (SOPS) interviews will be video-taped for review by [redacted].

11 The BACS SC and HVLT-R are paper assessments. The paper BACS SC at Visit 23 is a different version than the BACS SC in the BAC App that is also completed at Visit 23.

12 Patients who do not speak English will take the pen-and-paper Brief Assessment of Cognition Schizophrenia (BACS) available in their native language.

13 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 to administer SOPS. See Section 6.2.2. Columns are shaded in grey in the Flow Chart to indicate phone visits.

14 The Columbia Suicide Severity Rating Scale (C-SSRS) Baseline/Screening version will be used at Visit 1 (Screening Visit). At other scheduled visits, the C-SSRS Since Last Visit version will be used. The screening eC-SSRS report must be reviewed by the investigator/qualified rater for validity prior to randomization.

15 The PANSS should also be administered at the time conversion to psychosis is diagnosed.

16 To confirm eligibility prior to start of the study treatment.

17 The first dose administration must be done on Day 1 at the site after all baseline assessments are completed.

18 Patients have the option of identifying an informant to provide ratings for the Schizophrenia Cognition Rating Scale (SCoRS). In person ratings are preferred whenever possible. However, if the informant is not available for in person ratings, telephone interview is acceptable.

19 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.

20 Psychosis events after randomisation are Outcome Events. See Section 5.3.6.3.

21 The NAPLS risk calculator score will be calculated and data entered by [redacted].

22 Patients who have prematurely discontinued study drug and have not continued making regular visits (in person or phone) must have Vital Status collected approximately one year after the patient was randomized.

TABLE OF CONTENTS

ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
ALT	Alanine transaminase (SGPT)
ANOVA	Analysis of variance
APS	Attenuated Psychosis Syndrome
ARMS	At Risk Mental State
ASSR	Auditory steady-state response
AST	Asparatate transaminase (SGOT)
BAC App	Tablet based Brief Assessment of Cognition
BACS	Brief Assessment of Cognition in Schizophrenia
BACS SC	Brief Assessment of Cognition in Schizophrenia: Symbol Coding
BCVA	Best Corrected Visual Acuity
BDNF	Brain-derived neurotrophic factor
BI	Boehringer Ingelheim.
b.i.d.	bis in die (twice daily dosing)
Bpm	Beats per minute
CA	Competent Authority
[redacted]	[redacted]
CHR	Clinical High Risk
CI	Confidence Interval
cGMP	Cyclic guanosine monophosphate
CML	Local Clinical Monitor
CNS	Central Nervous System
COPS	Criteria Of Psychosis-risk Syndromes
CRA	Clinical Research Associate
CRF	Case Report Form
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
DALY	Disability adjusted life year
dB	decibel
DDI	Drug-drug interaction
DEDP	Drug exposure during pregnancy
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram

eC-SSRS	Electronic Columbia Suicide Severity Rating Scale
EDC	Electronic Data Capture
EEG	Electroencephalogram/Electroencephalography
EM	Extensive metabolizers
[redacted]	
EOT	End of treatment
ERP	Event related potential
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEP	First episode of psychosis
Fluency	Category Fluency: Animal Naming
F-M 100	Farnsworth-Munsell 100 hue test
$GABA_A$	gamma-aminobutryic acid
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
GF: Social	Global Functioning: Social
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HrQoL	Health related quality of life
HVLT-R	Hopkins Verbal Learning Test-Revised
HZ	Hertz (frequency)
IB	Investigator's Brochure
ICC	Intra-class correlation coefficient
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-6	Interleukin 6
IL 1β	Interleukin 1 beta
IQ	Intelligence Quotient
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IPEG	International Pharmaco-EEG Society
ITC	Inter-trial phase coherence
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
LNS	Letter-Number Span
LTP	Long term potentiation
MATRICS	Measurement And Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MedDRA	Medical Dictionary for Drug Regulatory Activities
[redacted]	
MEG	Magneto-encephalography
MMN	Mismatch negativity
MMRM	Mixed effects model with repeated measurements

MoA	Mechanism of Action
Ms	millisecond
NAPLS	North American Prodromal Longitudinal Study
NIMH	National Institute of Mental Heath
NMDA	N-methyl-D-aspartate
OPU	Operative Unit
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PD	Pharmacodynamics
PDE9	Phosphodiesterase-9
[redacted]	
PI	Principal Investigator
PK	Pharmacokinetics
PM	Poor metabolizers
p.o.	per os (oral)
POPS	Presence Of Psychosis Scale
q.d.	quaque die (once a day)
qEEG	Quantitative EEG
REML	Restricted maximum likelihood
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RON	Reorienting negativity
SAE	Serious Adverse Event
SCoRS	Schizophrenia Cognition Rating Scale
SIPS	Structured Interview for Psychosis-Risk Syndromes
SOP	Standard Operating Procedure
SOPS	Scale of Prodromal Symptoms
SPET	Single photon emission tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Trial Clinical Monitor
TES	Total error score
TNFα	Tumor necrosis factor alpha
TS	Treated set
TSAP	Trial Statistical Analysis Plan
TMT	Trail Making Test TMT
UHR	Ultra High Risk
ULN	Upper limit of normal
URS	User Requirement Specifications
VAS	Visual analogue scale
WHO	World Health Organization
YLD	Years lived with disability

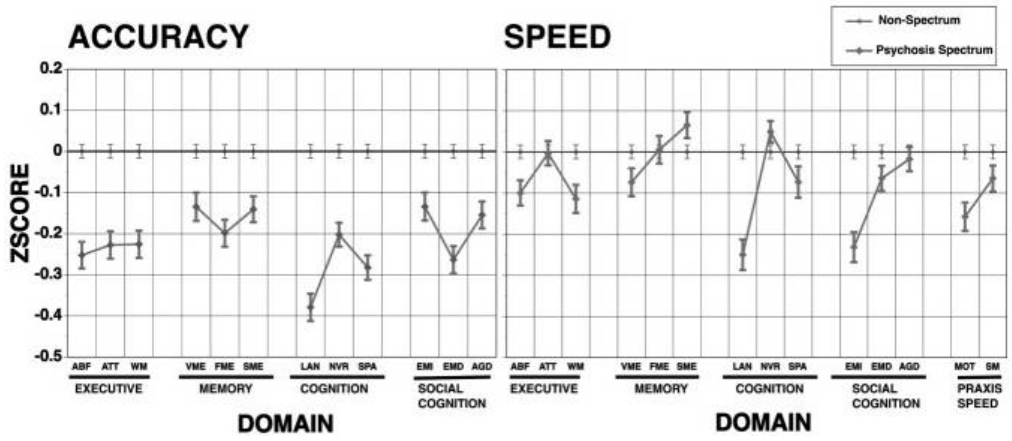
1. INTRODUCTION

BI 409306 is a Phosphodiesterase-9 (PDE9) inhibitor under development for the prevention of relapse in persons with schizophrenia, and for the treatment of patients with attenuated psychosis syndrome (APS) [c01694347-08].

1.1 MEDICAL BACKGROUND

Over the past decade, research into the factors that contribute to the development of psychosis has led to the awareness that subgroups of patients can be identified, including individuals <18 years of age, in whom conversion to overt psychosis is likely to occur [R15-1442, R15-1790]. Moreover, the presence of non-specific psychosis spectrum symptoms has indicated that incidence rates for comorbid mental disorders in adolescents are almost twice the incidence found among the general U.S. population [R15-1442]. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), proposes the classification of Attenuated Psychosis Syndrome (APS) as a condition for further study, identifying a vulnerable group of individuals suffering from "manifest pathology and impaired function and distress" [R15-4424]. This subgroup of clinically high risk (CHR) individuals exhibits discernible motor, emotional, cognitive, and behavioral alterations that are intermediate between those of healthy individuals and those with schizophrenia [R15-1442] (Figure 1.1:1). These at-risk individuals represent a population who stand to benefit from early detection and treatment of the aforementioned symptoms as well as possible prevention of subsequent psychotic conversion. Such symptoms as well as the occurrence of psychotic episodes are the focus of the investigation plan for BI 409306.

Figure 1.1:1 Computerized Neurocognitive Battery profiles of psychosis spectrum and non-spectrum physically healthy youths[1].



[1]ABF – abstraction/flexibility, ATT – attention, WM – working memory, VME – verbal memory, FME – face memory, SME – spatial memory, LAN – language, NVR – non-verbal reasoning, SPA – spatial processing, EMI – emotion identification, EMD – emotion differentiation, AGD – age discrimination, MOT – motor, SM – sensorimotor

The clinically high risk (CHR) state has been the focus of extensive research over the last decade and was described in the DSM-5 as Attenuated Psychosis Syndrome (APS), alternatively called "ultra-high risk" (UHR) and "at-risk mental state" (ARMS). There is broad consensus of the existence of a prodromal, at-risk syndrome as well as hypotheses regarding potential intervention [R15-1790, R15-1792].

Community based-epidemiology data were published from the Philadelphia Neurodevelopmental Cohort, a collaborative investigation of clinical and neurobehavioral phenotypes in a prospectively accrued cohort of youths (ages 11-21; N=7,054). Among medically healthy youths, 3.7% reported threshold psychotic symptoms (delusions and/or hallucinations). An additional 12.3% reported significant sub-psychotic positive symptoms, with odd/unusual thoughts and auditory perceptions, followed by reality confusion, being the most discriminating and widely endorsed attenuated symptoms [R15-1442]. These data suggest not only that psychosis is substantially prevalent among youth, but in addition, the vulnerability for psychosis and dysfunction associated with high-risk symptoms, is widely present.

Data from a recent analysis of a large US insurance claims database (R18-0654) demonstrated that as far back as five years before an incident diagnosis of schizophrenia subjects presented for care and utilized healthcare resources at a rate twice that of age and region matched controls. The data demonstrated that these individuals are prescribed a number of medications including antipsychotics and antidepressants, suggesting that their level of symptomatology has already become problematic in their lives.

Recently, several studies have evaluated the potential applicability of methods to detect and prevent psychosis [R15-1790, R15-1442, R15-1792]. New psychometric instruments have been developed to better predict the appearance of FEP in a CHR population. Recently, the North American Prodromal Longitudinal Study (NAPLS) consortium has reported development and validation of prodromal risk syndrome criteria which predict a 35% risk of conversion to psychosis within 2 ½ years of ascertainment [R15-1441, R15-1440]. The results have been used to develop a pilot, web-based individualized risk prediction tool that can be used to predict conversion risk based on profiles of risk factors for newly ascertained cases. Similar studies (e.g., ongoing [redacted] initiative in EU [www.[redacted].eu]; Personalised Prognostic Tools for Early Psychosis Management) have shown slightly different conversion rates, mainly due to aspects of diagnosis and definitions, which has led the United States (US) National Institute of Mental Health (NIMH) to initiate a project called HARMONY to align the different initiatives (www.nimh.nih.gov).

In the Global Burden of Disease 2000 study, published in the World Health Report 2001, schizophrenia is the 7th leading cause of years lived with disability (YLD) at a global level, accounting for 2.8% of total global YLD. Further, the Disability Adjusted Life Years (DALYs), reflecting the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability is estimated at 15.6 million [R16-5173]. In the "Global Burden of Disease Study 2010", 1160 sequelae of over 220 diseases were studied: the health state with the highest disability weight was acute schizophrenia [R13-0284]. No treatment exists that is shown to reduce the annual incidence of this devastating illness.

1.2 DRUG PROFILE

BI 409306 is a new chemical entity intended for oral administration. Film coated immediate release tablets of 50 mg 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 was 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) [c01694347-08]).

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 (for details please refer to section 5.2 of the IB [c01694347-08].

BI 409306 was tested in a comprehensive panel of in vitro and in vivo General Pharmacology tests (non-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 [c01694347-08].

Clinical Summary

In all 10 healthy volunteer trials, the most frequent drug related adverse events were visual side effects that occurred shortly after dosing, mostly resolved within 1 hour, 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 [c01694347-08]. 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 350 mg in CYP2C19 extensive metabolizers (EM); up to 100 mg in CYP2C19 poor metabolizers (PM)) in healthy young volunteers and multiple doses (14 days up to 100 mg EM/50 mg 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 [c01694347-08].

Study 1289.18 was conducted to assess safety, tolerability, PK and pharmacodynamics (PD) of BI 409306 25 mg, 50 mg, or 100 mg QD 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 cognitive impairment associated with schizophrenia) 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 adverse event (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 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 subject 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 [c01694347-08; c09991178-01].

Subsequent pharmacometric modelling was conducted simulating PK and PD in 2000 subjects and showed that a dose of 50 mg b.i.d. would provide exposures of >65 nM (1xIC50) in 93% of subjects for 5.9 hours twice a day compared with 49% of subjects for 4 hours in subjects receiving the 25 mg QD dose. Therefore we conclude that a dose of 50 mg

b.i.d. provides optimal exposure levels within the CSF while demonstrating acceptable tolerability.

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) [c01694347-08].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

PDE9 inhibition is hypothesized to improve the N-methyl-D-asparate acid (NMDA)-receptor signaling cascade by increasing cyclic guanosine monophosphate (cGMP) levels with subsequent lead to strengthening of synaptic plasticity as measured by enhanced hippocampal long-term potentiation (LTP) [c01694347-08]. Increasing evidence suggests that glutamatergic dysfunction may play a key role in mediating risk for conversion to psychosis [P15-03385, R15-3282, R15-1561]. Reorganization of synapses occurs extensively during postnatal and adolescent brain development until young adulthood, and one of the major changes is reorganization of glutamatergic synapses in which the NMDA receptor plays a key role. This important neurodevelopmental process results in changes in brain plasticity and synaptic transmission, known as synaptic pruning, since synapses are reorganized into more efficient configurations and weak connections are being eliminated [R15-1457, R15-3301]. Consistent with this, total gray matter volume in cortical areas was found to increase at earlier ages, followed by sustained loss starting around puberty as revealed in magnetic resonance imaging studies [R15-1783, R15-3396]. Regarding schizophrenia, plausible scenarios of its genesis includes “faulty” over-pruning later during adolescence [R15-1563, R15-3331] which is in-line with changes in NMDA receptor density (especially NR1 subunit decrease) seen in post-mortem brain from patients with schizophrenia [R15-1784, R15-1789] and in single photon emission tomography (SPET) studies in patients [R15-1786].

Synaptic over-pruning (i.e. elimination of important as well as less-relevant synaptic connections likely due to NMDA receptor dysfunction) during synaptic reorganization of the brain in adolescence remains an untested candidate pathogenic mechanism underlying transition from states of attenuated psychosis syndrome to frank psychosis. Synaptic pruning targets weak synapses, but synapses are strengthened with experience via mechanisms of synaptic plasticity, including NMDA receptor dependent signaling LTP. Thus, it is hypothesized that synaptic over-pruning compromises synaptic plasticity/LTP, which may further exacerbate deficient plasticity and intensify over-pruning [R15-1457]. Regarding strengthening of synaptic plasticity, BI 409306 [c01694347-08] and other PDE9 inhibitors such as PF-04447943 [R15-3303] showed an enhancement of hippocampal LTP. Moreover, studies of exposure of hippocampal neurons to the PDE9 inhibitor PF-04447943 demonstrated both enhanced neurite outgrowth and an increase in the number of synapses per neurons [R15-3303], providing evidence of a putative mechanism of action (MoA) for alleviating synaptic over-pruning in addition to strengthening of synaptic plasticity, thus suggesting a rational target for early intervention in APS, as well as that for cognitive impairment associated with schizophrenia.

In conclusion, these preclinical and clinical findings suggest that inhibition of PDE9 by BI 409306 represents a rational approach for improvement and potentially normalization of those processes dysfunctional in individuals with attenuated psychosis syndrome, leading to reduction or remission of the symptoms, and the delay or even prevention of FEP in

individuals with attenuated psychosis syndrome via decreasing synaptic over-pruning and strengthening the NMDA-receptor signaling and synaptic plasticity.

This trial is a proof of concept study designed to investigate the effect of BI 409306 on early intervention in patients with APS. Adolescents (≥16 years old) will be included in this trial based on the recognition that the clinically high-risk state is already apparent in this age group and the criteria and symptomatology in adolescents under 18 is identical to the presentation of the older (>18) individuals.

2.2 TRIAL OBJECTIVES

The objective of this study is to investigate the efficacy, safety and tolerability of BI 409306 compared to placebo given for 52 weeks to patients with attenuated psychosis syndrome. The study is designed to show superiority of BI 409306 over placebo in achieving remission of APS as well as improvement in cognition and functional capacity.

Exploratory biomarkers will be evaluated including NMDA-R signaling genotyping, salivary cortisol, brain-derived neurotrophic factor (BDNF), inflammatory cytokines in the blood, and automated speech analysis to explore their association with clinical outcome in patients with attenuated psychosis syndrome.

An optional electroencephalogram (EEG) sub-study will investigate the clinical utility of quantitative EEG, and auditory and visual event related potential (ERP) biomarkers for risk stratification and targeted intervention. See Section 10.1.

A subset of patients will complete ocular safety tests to further characterize the ocular safety of BI 409306. See Section 10.2.

2.3 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 10 mg, 25 mg and 50 mg 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 [c09991178-01]. 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. All adverse effects generally were restricted to high dose levels and were reversible [U12-1034; U13-1182; U12-2165; U13-1303]. Cardiac function will be monitored during the study according to the Flow Chart.

It is expected that the metabolic clearance of BI 409306 will be similar for adolescents and adults. Any possible effects on sexual maturation will be monitored clinically via appropriate endocrine markers. Inclusion of adolescents in this trial is based on the recognition that the clinically high-risk state is already apparent in these adolescents and the criteria and symptomatology in adolescents under 18 is identical to the presentation of the older individuals.

As with all drugs, the potential for hypersensitivity and allergic reactions have to be taken into consideration when BI 409306 is administered. Other risks are inherent to any clinical trial such as unexpected adverse clinical or laboratory events. 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 5.3.6.1.

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 [c01694347-08].

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 [c01694347-08].

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. This must be balanced with an effort to ensure that the population under study is representative to the extent possible, of the population intended to be prescribed the compound, should it ever receive regulatory approval. Since suicidality is known to be common in the CHR population, the exclusion criteria for this study allow for an assessment of past suicidal behaviour by the investigator while excluding recent significant suicidal ideation. 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.

NAPLS has constructed an algorithm to estimate the risk of conversion to psychosis depending on several risk factors. When applied, this algorithm predicts the conversion rates for patients without treatment [R16-3564]. This algorithm will be utilized to assess the sample of eligible patients to better quantify risk for conversion. Patients who convert to psychosis will continue to be followed in the trial.

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. All randomised patients will receive Brief Supportive Psychoeducation, which was developed for use within the NAPLS studies and demonstrated statistically significant improvement in positive symptoms over six months compared to baseline [R16-1547]. Patients are also permitted to remain on any psychotropic medications and new concomitant medications may be prescribed as necessary to ensure the welfare of the patient. 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.

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, 300 patients with Attenuated Psychosis Syndrome (APS) are planned for randomisation in this study.

Patients are included in the study once informed consent/assent has been signed. Patients suitable after screening will be randomised to the 52 week treatment period assigned at a ratio of 1:1 to one of two treatment groups as shown in Figure 3.1: 1. Randomisation will be stratified by baseline use of antipsychotics (see Section 7.6 for details). After completion of the treatment period, or following early discontinuation, patients will complete the 4 week follow-up period.

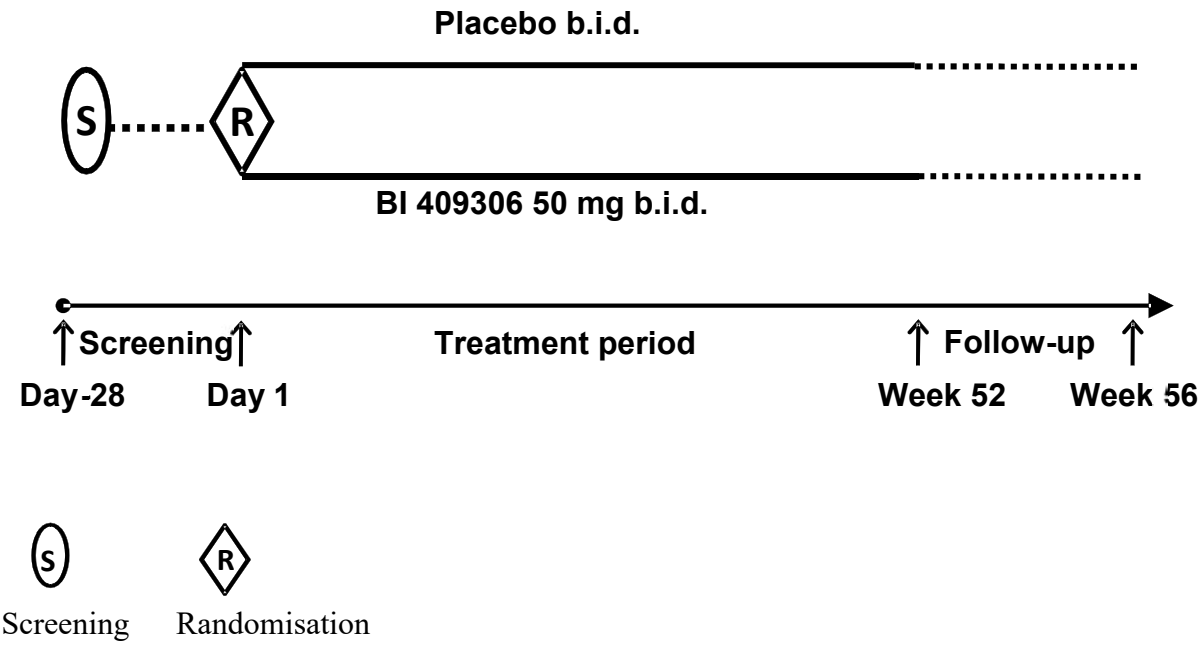


Figure 3.1: 1 Overview of trial design

Additionally, exploratory biomarkers will be assessed for structural and functional measures of brain plasticity. These objective markers of brain physiology may help interpretation of the data or may help identify subgroups of patients that are better responders. The Biomarker Plan is described in Section 5.5.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI). Boehringer Ingelheim has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal standard operation procedures (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 internal 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. For these activities, a Trial Data Manager and Trial Statistician have been appointed.

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 Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators and other important participants, including 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 an electronic ISF.

A data-monitoring committee (DMC) independent of the sponsor will be established to assess the progress of the clinical trial and to ensure there is no imbalance in safety endpoints. The DMC will meet three times per year. An unblinded safety and efficacy assessment is planned to recommend to the sponsor whether to continue, modify, or stop the trial. Measures are in place to ensure blinding of the sponsor and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings, which will be stored as per the charter.

[redacted] has been selected as a service provider to support the following tasks related to the instruments and scales for patient assessment: rater prequalification, rater training, provision of rater materials, and central review of assessments for quality (SIPS/ SOPS, HVLT-R, BACS SC, BAC App, SCoRS). These responsibilities and tasks will be defined in a written contract before initiation of the clinical trial.

[redacted] will confirm each patient's diagnosis of Attenuated Psychosis Syndrome (APS) after review of the video-taped Structured Interview for Psychosis-Risk Syndromes (SIPS) during the screening period. A Central Rating Committee will adjudicate conversions to psychosis after [redacted]' review of the video-taped Scale of Prodromal Symptoms (SOPS) interviews. After the video and source document review has been completed, site and sponsor personnel will receive feedback on the interview quality and ratings. The tasks and responsibilities of [redacted] and the Central Rating Committee will be specified in the Assessment Procedures Binder, including documentation specifications regarding the SIPS/SOPS review.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in an IRT Manual and Central Laboratory Manual, filed in the ISF. Vendors will also be used to administer the suicidality assessment (eC-SSRS) via telephone and to monitor medication adherence using a smartphone application.

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 on the remission of APS symptoms as well as improvement in cognition and functional capacity. The primary efficacy analysis is planned to be conducted after 52 weeks of treatment. The 4-week 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 indicated for the treatment of symptoms of APS or for the prevention of first episode of psychosis. 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 their concomitant psychotropic medications, will receive Brief Supportive Psychoeducation, and are permitted to receive a new or increased dose of antipsychotic medication if the Principal Investigator (PI) feels the patient has experienced a first episode of psychosis. The risk to the control group is discussed in Section 2.3.

3.3 SELECTION OF TRIAL POPULATION

It is planned that approximately 50 trial centres in up to four countries will be participating in this trial to randomise 300 patients. Eligible patients will be randomised to the 52 week treatment period assigned at a ratio of 1:1 (BI 409306 50 mg b.i.d. (twice daily dosing), placebo).

It is expected that approximately 6 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 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 CML, and documentation of approval filed in the 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/assent) 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 meeting the following diagnostic criteria for attenuated psychosis syndrome (APS) as defined in DSM-5 will be included:

A. At least one of the following of symptoms is present in attenuated form, with relatively intact reality testing and is of sufficient severity or frequency to warrant clinical attention:
   - Delusions
   - Hallucinations
   - Disorganized speech.
B. Symptom(s) must have been present at least once per week in the last 1 month
C. Symptom(s) must have begun or worsened in the past year
D. Symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention
E. Symptom(s) is not better explained by another mental disorder, including: Depressive or bipolar disorder with psychotic features and is not attributable to physiological effects of a substance or another medical condition
F. Criteria for any psychotic disorder have never been met.

A diagnosis of Attenuated Positive Symptom Syndrome is defined by the presence of recent attenuated positive symptoms that meet ALL of 5 criteria: sufficient **severity** (criterion A), sufficient **frequency** (criterion B), **recency** of onset or worsening (criterion C), associated with sufficient distress or disability to warrant clinical attention ("**warrant attention** criterion," criterion D), and not have been likely due to another disorder ("**attribution** criterion," criterion E).

Patients may be enrolled if they are currently taking antipsychotic medication (See Section 4.2.1). If a patient discontinues an antipsychotic medication, they can be randomized two weeks after discontinuation.

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. Meet diagnostic criteria for attenuated psychosis syndrome as defined in DSM-5 and determined by SIPS administered at screening and diagnosis confirmed by [redacted] after review of video-taped SIPS interview.
2. *Inclusion criterion 2 removed in global amendment 3. Numbering of subsequent criteria was not changed.*
3. Age ≥16 and ≤ 30 years at the time of consent/assent.
4. Male or female patients willing to use highly effective methods of contraception.
   - 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.
5. Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to any study-related procedures OR signed and dated informed consent provided by the patient's parent(s) (or legal guardian) and assent by the patient prior to any study-related procedures in accordance with GCP and local legislation[2]. If the patient has a legal representative, then this legal representative must give written informed consent as well.

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1. Females of childbearing potential are defined as:
   - fertile, following menarche and until becoming post-menopausal unless permanently sterile.
   - not postmenopausal (12 months with no menses without an alternative medical cause) and
   - not permanently sterilised (e.g., hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

2. Patients who sign the assent and reach the age of majority during the trial must sign the current version of the informed consent.

3.3.3 Exclusion criteria

1. Present or past diagnosis of schizophrenia, schizophreniform, schizoaffective disorder, bipolar disorder I, major depressive disorder with psychotic features, delusional disorder, brief psychotic disorder, other specified schizophrenia spectrum and other psychotic disorder (except attenuated psychosis syndrome), and unspecified schizophrenia spectrum and other psychotic disorder, according to DSM-5.
2. Patients taking antipsychotic medication for less than 8 weeks, or patients taking antipsychotic medication for a longer duration but who have not been on a stable dose for 8 weeks prior to informed consent.
3. Patients who begin taking an antipsychotic between Visit 1 and Visit 2.
4. Patients who have discontinued an antipsychotic medication less than two weeks prior to randomization.
5. Patients taking Clozapine.
6. Suicidal behavior in the past 2 years reported in the Columbia Suicide Severity Rating Scale (C-SSRS) with a lethality of attempt ≥1, or with a lethality of 0 but a potential lethality of 2, or that in the judgement of the investigator would jeopardize the patient's safety while participating in the trial. The investigator/qualified rater must review all screening C-SSRS reports prior to randomization, documenting an additional interview assessing lethality of the behavior history when appropriate.
7. 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).
8. 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.
9. Known diseases of the central nervous system (including but not limited to any kind of seizures or stroke).
10. History of significant head injury (>5 minutes without consciousness).
11. A serious developmental disorder that in the judgement of the investigator would inhibit the patient's ability to comply with all study procedures, or mental retardation (documented IQ <70), or acute attenuated symptoms exclusively related to intoxication from a psychotropic substance.
12. 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.
13. Planned elective surgery requiring general anesthesia, or hospitalization for more than 1 day during the study period.
14. Meets criteria for Substance Use Disorder (DSM-5) within the six months prior to informed consent/assent.
15. 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.
16. Patients taking strong or moderate CYP1A2 inhibitors who are also a CYP2C19 Poor Metabolizer (PM). Patients taking medication known to be a strong or moderate inhibitor 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.).

17. 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.)
18. Patients with a history of moderate to severe hepatic impairment (Child-Pugh B / C).
19. Patients with a history of moderate to severe renal impairment (Stage 3 – 5).
20. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
21. In the judgment of the investigator, inability of the patient to comply with the clinical trial procedures.
22. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).
23. Previous participation in any BI 409306 study.
24. Known hypersensitivity to the drug product excipients (lactose monohydrate, pregelatinized starch, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, talc and iron oxide yellow).

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

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

- The patient withdraws consent for trial treatment or trial participation, 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 adhere to the trial requirements in the future.
- The patient exhibits suicidality, in the clinical judgement of the Investigator or according to criteria below:
    - Any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)

- Any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)

Patients who discontinue participation after signing the informed consent/assent form but prior to randomisation (Visit 2) will be considered screening failures.

Patients who discontinue or withdraw from the study after randomisation (Visit 2) will be considered as "early discontinuations" and the reason for premature discontinuation must be recorded in the electronic case report forms (eCRFs). Patients who withdraw or discontinue from the trial after randomisation will not be replaced. The data will be included in the trial database and will be reported.

Premature study drug discontinuation

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 Section 6.2.2. Patients who discontinue study drug prematurely should ideally be observed until the end of the study (week 52) as if they were still receiving blinded study treatment.

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 (in-clinic and phone 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: the SOPS Positive Symptom items, eC-SSRS, AEs, concomitant therapy (including change in dose or new dose of antipsychotic medication).
Early D/C Option 3	Discontinue participation in remaining study activities but permit collection of the occurrence of psychiatric illness and vital status approximately one year after randomization from 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 and vital status approximately one year after randomization 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. In this case, the patient does not need to justify the decision and should be withdrawn from the study and all follow-up assessments.

If the patient refuses all four options and elects to immediately discontinue the trial, the patient should complete the same EOT and follow-up procedures as those patients who choose Early D/C Options 3 and 4. Completing these procedures is strongly recommended for the patient's safety.

The discussion with the patient and the outcome regarding follow up, psychiatric and vital status collection, discontinuation of trial medication, and withdrawal of consent must be documented in the patient's medical records.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

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

Each film-coated tablet contains 50 mg BI 409306.

Eligible patients are randomly assigned to double blind treatment at a ratio of 1:1 of placebo or 50 mg b.i.d. BI 409306 (c.f. Section 4.1.4 and Table 4.1.4:1).

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:	50 mg
Posology	b.i.d.
Route of administration:	Oral

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

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

4.1.2 Selection of dose in the trial

Based on the effective doses in the T-maze spontaneous alternation test, the novel object recognition test in mice and clinical data of a cerebrospinal fluid (CSF) study in healthy volunteers, the therapeutic dose in humans was projected to be in the range of CSF exposure of 1xPDE9 IC50 corresponding to a dose in the range of 25 mg [c01694347-08]. Recent pharmacometric modelling indicates that a single dose of 25 mg once daily (q.d.) will result in therapeutic exposures in the CSF (1xIC50) in 49% of subjects over a 4 hour duration, while a 50 mg dose would result in 93% of subjects reaching such a CSF exposure for 5.9 hours. In line with the proposed mode of action, it is hypothesized that compounds which strengthen NMDA receptor signalling and LTP, exert long-lasting cognitive improvement in vivo outlasting drug exposure, therefore, a b.i.d. posology is 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 50 mg b.i.d. or placebo in a 1:1 ratio according to a randomisation plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

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/assent 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 two 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 one tablet of BI 409306 or placebo in the morning and one tablet of BI 409306 or placebo in the evening depending on the treatment group.

Table 4.1.4: 1 Treatment administration per dose group and day

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

Patients should be instructed to take their study medication with water at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food. BI 409306 tablets should not be chewed or crushed. If a dose is missed by more than 6 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.

4.1.5.2 Unblinding and breaking the code

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

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

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from [redacted] 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 will not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated 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.

Training kits containing placebo will be provided to allow for practice with the child-proof packaging.

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 trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator (if applicable)
- Availability of Form FDA 1572 (if applicable)

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

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the

sponsor and/or appointed CRO, the Investigator/Pharmacist/investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

If a patient is enrolled who is taking an antipsychotic medication that will continue during the treatment period, it is extremely important they continue to take the current antipsychotic medication at the same dose as when the patient was randomized. The dose of an antipsychotic medication can be decreased or discontinued entirely. A patient's dose of antipsychotic medication should be increased only in circumstances of significant worsening of psychosis symptoms that the investigator feels qualifies for a first episode of psychosis. Patients experiencing a first episode of psychosis should continue taking study drug at the discretion of the investigator.

When a patient begins a new prescription or increases their dose of an ongoing antipsychotic medication, this is an outcome event. The available information (e.g., SOPS interview video, medical records from prescribing physician) will be subsequently reviewed by the Central Rating Committee.

Antipsychotic 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. Prior and concomitant psychotherapy information should also be recorded in the eCRFs.

All patients (i.e., including those on BI 409306 and those on placebo) will receive Brief Supportive Psychoeducation at timepoints described in the Flow Chart. The supportive psychoeducation sessions will be administered by trained site staff and will educate patients and family members about the symptoms of attenuated psychosis syndrome as well as the clinical trial program, risk and protective factors, the impact of stress and the importance of medication adherence. Through these sessions, the patient's and family's needs are evaluated, a symptom reduction plan is developed and referrals for community services may be provided. Refer to Psychoeducation Manual and Materials in ISF.

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 medications known to be strong or moderate CYP1A2 inhibitors is 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 randomization, at the discretion of the 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.

Any medication that may interfere with the action of BI 409306 or whose action may be altered by concomitant administration of BI 409306 during the treatment period and the 4-week 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 in the opinion of the investigator. Urine drug screens for amphetamines, cannabis, cocaine, methadone, opiates, and phencyclidine (PCP) will be conducted during the trial for review by the Investigator. Patients with positive drug screens may remain in the trial at the discretion of the investigator.

Patients will be instructed to refrain from caffeine, alcohol, dairy products, and nonprescription medications the evening before and the morning of salivary cortisol sampling. Other than the visits with saliva collection, 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 Section 3.3.2.

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 in the investigator site file.

This trial will utilize a medication adherence monitoring platform ("Platform"). The Platform uses artificial intelligence on smartphones to confirm study medication ingestion. In addition, built-in reminders and a communication system allow 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 monitoring Platform requires that patients take each dose of the study medication while using a smartphone. The Platform will be provided to a patient preloaded on a smartphone or patients will download the Platform onto their own mobile device.

Patients will receive reminders within predefined time windows to take their medication using the Platform. This notification reminds patients to take their medication dose while 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 application 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. The amount of guidance that the device provides to the patient is automatically reduced as the patient becomes more proficient at using the application.

After the device confirms proper study medication ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrolment and improving the predictive algorithms, accuracy or usability of the Platform. The captured data and video is reviewable through a roles and rules restricted system ensuring privacy of the information. The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA) in the US, as well as UK and EU data protection regulations, which protect the privacy and security of healthcare 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 be provided with patient names, nor will they be given access to patient medical records.

The Platform will allow for rapid and tailored intervention in case of non-adherence (drug interruptions) without having to visit the clinic for unscheduled visits. 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 patient's source and on the appropriate eCRFs.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is time to remission from APS within a 52 week timeframe.

Per DSM-V, the proposed diagnostic criteria for APS are:

A. At least one of the following of symptoms is present in attenuated form, with relatively intact reality testing and is of sufficient severity or frequency to warrant clinical attention:
   - Delusions
   - Hallucinations
   - Disorganized speech.

B. Symptom(s) must have been present at least once per week in the last 1 month

C. Symptom(s) must have begun or worsened in the past year

D. Symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention

E. Symptom(s) is not better explained by another mental disorder, including: Depressive or bipolar disorder with psychotic features and is not attributable to physiological effects of a substance or another medical condition

F. Criteria for any psychotic disorder have never been met.

A diagnosis of APS is defined by the presence of recent attenuated positive symptoms that meet ALL of 5 criteria: sufficient **severity** (criterion A), sufficient **frequency** (criterion B), **recency** of onset or worsening (criterion C), associated with sufficient distress or disability to warrant clinical attention ("**warrant attention** criterion," criterion D), and not likely due to another disorder ("**attribution** criterion," criterion E).

A patient in remission is defined as someone who no longer meets the severity criterion.

Remission from APS is defined as a score of <3 on all of the P1-P5 Positive Symptom items of the SOPS and maintained until the end of treatment.

5.1.2 Secondary Endpoints

- Time to first episode of psychosis within a 52 week timeframe as adjudicated by the Central Rating Committee. First episode of psychosis defined as one or more SOPS P1-P5 rated a 6 AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month. OR a new prescription or increase in dose of an ongoing antipsychotic medication. Time of onset of first episode psychosis is defined using the rater's best estimate as determined in the SOPS interview or when

the patient began taking a new prescription or increased the dose of antipsychotic medication.

- Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 24 and 52 weeks of treatment.
- Change from baseline in the BAC App composite T score after 52 weeks of treatment.
- Change from baseline in Positive and Negative Syndrome Scale (PANSS) positive items score, negative items score, and total score after 52 weeks of treatment.

5.2 ASSESSMENT OF EFFICACY

Remission of APS, conversion to psychosis, functional capacity, cognitive function, and disease state will be measured by the batteries and questionnaires listed below:

The Structured Interview of Psychosis-Risk Syndromes (SIPS) is a structured interview for diagnosing a clinical high risk (CHR) syndrome for psychosis and cases of first episode psychosis [R16-0681]. It contains a severity rating scale (Scale Of Prodromal Symptoms, or SOPS), a well-anchored Global Assessment of Functioning (GAF) [R16-0594], the DSM-5 schizotypal personality disorder checklist, a brief assessment of the family history of psychosis, the Criteria Of Psychosis-risk Syndromes (COPS) and Presence Of Psychosis Scale (POPS) and DSM-5 Attenuated Psychosis Syndrome criterion sets.

The **SOPS**, contained within the SIPS, assesses Positive, Negative, Disorganization and General symptoms. It is administered as a semi-structured interview with 19 rating scales measuring severity and change of prodromal symptoms. Each item is scored from 0-6. The positive symptoms are scaled from 0 (absent) to 6 (severe and psychotic). The remaining items are scaled from 0 (absent) to 6 (extreme). The 19 rating scales are each independently anchored.

The Positive scale is used to make a diagnosis of attenuated psychosis syndrome (APS) and conversion to psychosis. To meet criteria for APS, a patient must at some point have rated level “3”, “4”, or “5” on at least one of the P1-P5 Positive Symptom items of the SOPS. The symptom(s) must have occurred at the then-current intensity level at an average frequency of at least once per week in the past month, and must not have been likely due to another disorder. The Negative, Disorganization and General domains are used to assess the severity of the diagnosis [R15-1441].

Conversion to psychosis and time to conversion will be adjudicated by the Central Rating Committee after review of video-taped SOPS interview. Adjudication will take into account information provided by patients, informants, and medical records when available.

Schizophrenia Cognition Rating Scale (SCoRS) will be used to evaluate everyday functional capacity.

The SCoRS is a 20-item interview-based assessment of cognitive deficits and the degree to which they affect day-to-day functions. It collects information from a patient interview, interview with an informant (if available), and the administering clinician.

The Schizophrenia Cognition Rating Scale (SCoRS) benefits from receiving information from an informant with frequent contact with the patient. However, it is not required and some patients may wish not to provide contact information for an informant. When conducting the SCoRS, in-person ratings are preferred whenever possible. The informant is any person who interacts with the patient at least 2 times per week.

Each of the 20 items of the SCoRS is rated on a 4-point scale. Higher ratings reflect a greater degree of impairment. The composite score will be the sum of the 20 items [R16-4322].

The Brief Assessment of Cognition in Schizophrenia (BACS) will be used to evaluate cognitive function. There are two versions of the BACS available: the traditional pen-and-paper version and a **tablet based Brief Assessment of Cognition (BAC App)** [R17-0578]. The BACS consists of six tests assessing multiple domains of cognitive function: Verbal Memory, Digit Sequencing, Token Motor Task, Semantic and Letter Fluency, Symbol Coding, and Tower of London.

The BAC App will be used for English speaking patients. The BAC App provides digital recording of data, audio recordings of verbally-delivered responses, and examiner-recorded

data for post-test verification of responses. Patients who do not speak English will take the pen-and-paper BACS available in their native language.

A composite T score that is calculated using the six standardized scaled sub-test scores will be generated.

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 when possible. The total score is the summation of the 30 item scores [R13-5061].

The **Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS SC) and Hopkins Verbal Learning Test-Revised (HVLT-R)** will be used to evaluate the effects of BI 409306 on cognitive function, and are variables required for the NAPLS Risk Calculator. The BACS SC measures speed of processing. This timed test involves using a key to write digits that correspond to nonsense symbols. The BACS SC score is the total number of correct responses in 90 seconds.

The HVLT-R measures verbal learning. The patient is asked to recall words from a list of 12 words read orally by the Rater. There are three learning trials with each administration. Delayed recall and recognition will not be administered. The HVLT-R score is the total number of words correctly recalled across the three trials.

NAPLS Risk Calculator uses an algorithm designed to predict individualized risk of psychosis in clinical high-risk patients using demographic, clinical, neurocognitive, and psychosocial predictor variables. The web-based risk calculator generates a score representing the probability of transition to psychosis within the next 12 months. The predictor variables used in this study are:

- Age
- Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS SC)
- Hopkins Verbal Learning Test-Revised (HVLT-R)
- SIPS items P1 and P2 (unusual thought content and suspiciousness)

- Global Functioning: Social (assessment of decline in social functioning in the past year)

5.3 ASSESSMENT OF SAFETY

Physical examination, vital signs, laboratory tests, ECG, suicidality, extrapyramidal symptoms, and occurrence of (S)AEs will be assessed.

5.3.1 Physical examination

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

A physical examination including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system will be performed. The physical examination will include examination of known and suspected sites of disease.

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

5.3.2 Vital Signs

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

5.3.3 Safety laboratory parameters

All safety parameters that will be determined during the trial are listed in Table 5.3.3:1. Patients should be fasting for at least 8 hours prior to the blood samples taken at Visit 2 and Visit 23 or EOT. All analyses will be performed by a central laboratory. Instructions on collection, handling/ processing, and shipping of the samples will be provided in the lab manual by the central laboratory. For time points of laboratory sampling refer to the Flow Chart.

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

Table 5.3.3:1 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)
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
Chemistry (cont.)	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

Category	Test name
	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)
Endocrine	LH, FSH, testosterone, and estrogens (e.g. estradiol) (for randomised patients only)

5.3.4 Electrocardiogram

The 12-lead ECGs will be performed 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 significant, if abnormal. The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the patient's medical file if there is no validated and certified e-medical record for ECG data.

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

5.3.5 Other safety parameters

5.3.5.1 Assessment of suicidality

Suicidality should be monitored closely during the study period. Suicidal thoughts and behavior will be assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) (R08-1147). An electronic version (eC-SSRS) utilizing a telephone 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 computer-automated eC-SSRS is a self-rated version of the C-SSRS using a phone, Web or tablet device. Patients who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in about 3 minutes. Patients with significant suicidal ideation or behavior may require up to 10 minutes answering all relevant questions. This assessment should be conducted early in the visit to provide sufficient time for the report to be received at the trial site prior to patient departure. At the conclusion of each assessment, the site will receive an eC-SSRS Findings Report via email or fax. The report presents the findings for suicidal ideation, intensity of ideation, suicidal behavior, and lethality/medical damage (for actual suicide attempts only).

The C-SSRS/eC-SSRS has been widely used in large multinational clinical trials. The eC-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 life time 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. The investigator/qualified rater must perform and document an additional interview if there is doubt about the validity of the report. 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 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. See Section 5.3.6.

The patient should be withdrawn from treatment if the patient exhibits suicidality and meets the withdrawal criteria mentioned in Section 3.3.4.1.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation 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, this 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 prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgment 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.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior after the baseline visit 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 (see Section 5.3.5.1 for details).

AEs considered "Always Serious"

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 given above.

The latest list of "Always Serious AEs" can be found in the Electronic Data Capture (EDC) system. These events should always be reported as SAEs as described above.

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

Adverse events of special interest (AESIs)

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

No other AESIs have been defined for this trial.

Intensity of AEs

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

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, 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 study drug treatment continues or remains unchanged.

5.3.6.2 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 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 their patient files. The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent/assent onwards through the Residual Effect Period (REP), until individual patient's end of trial:
  -all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form, but not on the CRF.
  The rules for Adverse Event Reporting exemptions still apply, please see Section 5.3.6.3.

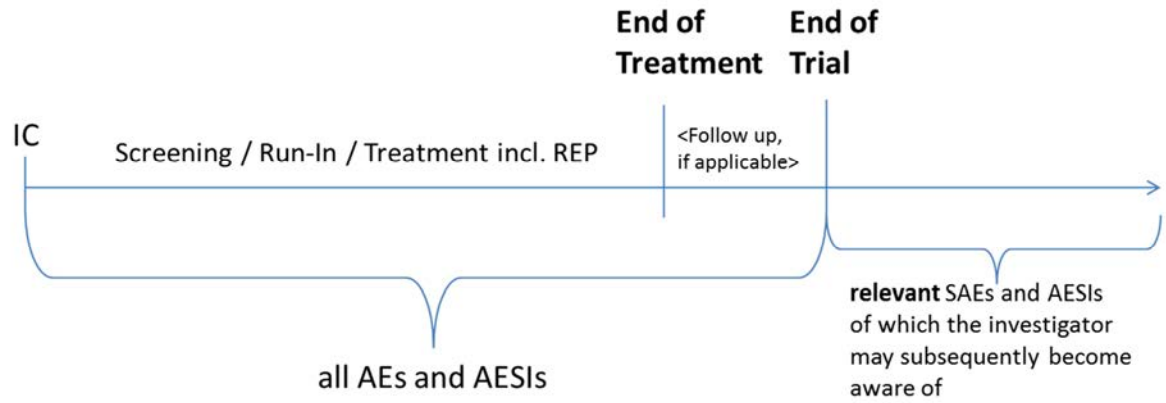

Figure 5.3.6.2: 1 AE Collection

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 only report relevant SAEs and relevant AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form, but not on the CRF.
The rules for Adverse Event Reporting exemptions still apply, please see Section 5.3.6.3.

The REP is defined as 7 days after the last dose of trial medication is taken. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment, please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines

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

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 CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

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

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

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

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

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

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

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

5.3.6.3 Exemptions to SAE reporting

Psychosis is considered an Outcome Event and is exempted from reporting as an SAE. See Section 5.1.2 for the definition of psychosis. However, when there is evidence suggesting a causal relationship between study drug and an episode of psychosis, the event must immediately be reported as an SAE on the SAE form and on the appropriate eCRF.

Psychosis events determined not related to study drug should be recorded on the appropriate pages of the eCRF as part of efficacy data collection. These outcome events will be collected, adjudicated by the Central Rating Committee, and monitored by the DMC.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

5.5 ASSESSMENT OF BIOMARKERS

This section refers to exploratory biomarkers.

5.5.1 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, incl. audit trail for clinical data and samples to identify and destroy such samples according to 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

5.5.1.1 Methods and Timing of Pharmacogenomic Sample Collection

Sampling will be performed at the time points specified in the Flow Chart. Approximately 8.5 mL 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.

5.5.2 Pre-specified Pharmacogenomic Analysis

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. 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 exploratory, prespecified 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. The sample will be used for DNA extraction and subsequent genotyping for variants in genes related to the disease and NMDA-R signaling, such as BDNF. Pre-specified analyses will be performed at the end of the trial and the data will be part of the clinical trial report.

All remaining samples will be destroyed no later than three months after the end of the trial.

Collection methods for the samples for pre-specified pharmacogenomic analyses at Visit 2 are identical to that of the optional DNA banking sample. Please refer to Section 5.5.1.1. Detailed instructions on sampling, preparation, processing, shipment and storage of the samples collected at screening for CYP2C19 genotyping are provided in the laboratory manual.

5.5.3 Cortisol and Inflammatory Cytokines

Salivary cortisol and blood inflammatory cytokines such as Interleukin 6 (IL-6), Interleukin 1 beta (IL 1β) and tumor necrosis factor alpha (TNFα) will be assessed as exploratory biomarkers at the visits indicated in the Flow Chart.

Cortisol levels vary across the day [R16-3638]. Multiple saliva samples for the cortisol assay will be obtained at three time points during each of the visits specified in the Flow Chart in order to derive an average and increase the reliability of the cortisol estimate. The first sample should be collected when the patient arrives at the site; the second and third saliva samples will be collected at approximately 1.5 hour intervals. If the patient has a meal or snack during the visit, samples should be collected an hour before or after eating. Care should be taken to collect samples at approximately the same times at each visit.

The purpose of collecting these samples is to explore the association between stress or inflammatory biomarkers and clinical outcome in patients with attenuated psychosis syndrome.

Detailed instructions for sampling, handling and shipment of samples are provided in the Laboratory Manual, filed in the ISF.

5.5.4 BDNF Levels

BDNF levels will be assessed from peripheral blood as an exploratory biomarker to investigate its potential in disease modulation and as an outcome related pharmacodynamic biomarker.

Blood samples will be collected at time points indicated in the Flow Chart.

Detailed instructions for sampling, handling and shipment of samples are provided in the Laboratory Manual, filed in the ISF.

5.5.5 Automated Speech Analysis

Automated speech analysis will be performed on audio-recorded patient interviews, comprising dream reports and short-term affective memories. Analysis will extract acoustic parameters from the speech data; generate speech graphs and semantic features from interview transcripts; apply classifiers to predict which patients will eventually develop psychosis by finding the optimal combination of acoustic, graph-theoretical and semantic features.

Patient interviews will be audio-recorded at the time points indicated in the Flow Chart.

Instructions for recording patient interviews are provided in an automated speech analysis procedures manual, filed in the ISF.

5.6 OTHER ASSESSMENTS

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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.

Each of the assessments (SIPS/SOPS, SCoRS, PANSS, BACS SC, HVLT-R and BAC App) should ideally be done by the same members of the site staff for a given patient throughout the study period. In addition, it is recommended that the BAC App and SCoRS not be administered to a patient by the same rater at the same visit to prevent bias on the SCoRS ratings.

Patients should start the BACS SC and HVLT-R assessments at the same time of day (±60 minutes) at each applicable visit. The start time of the BAC App assessment should also begin at the same time of day (±60 minutes) at each applicable visit. The BACS SC/HVLT-R and BAC App start times do not have to be within the same ±60 minute window. During the testing, patients are allowed to take short breaks as needed, in the judgment of the rater/investigator.

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/assent. After a patient has signed the informed consent/assent, 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/assent for the unspecified pharmacogenomics sample must be obtained if the patient is willing to provide the blood sample for DNA banking.

If the rater at the site concludes that the patient meets diagnostic criteria for APS, both the video-taped interview and the SIPS response forms must be reviewed and diagnosis

confirmed by [redacted] prior to randomisation. Please refer to the Assessment Procedures Binder for further information.

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/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

There is an optional, EEG sub-study that will enroll patients from a sub-group of study sites participating in the 1289-0032 study. Patients must provide a separate informed consent/assent prior to randomisation to participate in this study. See Section 10.

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 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.

Phone Visits are to be conducted at the time points specified in the Flow Chart to assess the overall status of the patient, check compliance, and to collect new AE and concomitant medication information. Patients will be instructed to complete the eC-SSRS, and site staff will confirm completion. If symptom worsening is suspected, an unscheduled in-clinic visit should be scheduled to further assess the patient as outlined below.

During the treatment period, all SIPS/SOPS assessments will be video-taped for review by the [redacted]. Please refer to the Assessment Procedures Binder.

Suspected First Episode of Psychosis:

If any Positive Symptom Score of 6/Severe and Psychotic is assigned while administering the SOPS, the following should occur:

- The PI should immediately contact [redacted] to arrange for expedited video review.
- PANSS should also be administered.
- Treatment should begin immediately if the PI feels this is necessary for the patient's safety.

If worsening psychotic symptoms are suspected during a phone visit, or if the patient reports a new prescription or increase in dose of an ongoing antipsychotic medication, the following should occur:

- Patient is to be scheduled for an unscheduled, in-clinic visit.
- Administer SOPS.
- If any Positive Symptom Score of 6/Severe and Psychotic is assigned while administering the SOPS, the PI should immediately contact [redacted] to arrange for expedited video review.
- PANSS should also be administered.
- Treatment should begin immediately if the PI feels this is necessary for the patient's safety.

If the patient is prescribed a new antipsychotic or has their ongoing antipsychotic dose increased by a physician other than the PI, medical records should be obtained for review by the Central Rating Committee.

Patients experiencing a first episode of psychosis should continue taking study drug at the discretion of the investigator.

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 in-clinic and phone visits, the following should be performed:

- EOT Visit should 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 for both in-clinic and phone visits through Visit 23.
- A Follow-Up Visit will not be performed.

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 should be performed within 7 days of last intake of study drug, or as soon as possible.
- A Follow-up Visit should be performed within 28 days of the EOT Visit.
- Thereafter, patients should be followed up over the phone according to the regular visit schedule through Visit 23.

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 should be performed within 7 days of last intake of study drug, or as soon as possible.
- A Follow-up visit should be conducted within 28 days of the EOT Visit.
- Occurrence of psychiatric illness and vital status must be collected approximately one year after the patient was randomized.

6.2.3 Follow Up Period and Trial Completion

Patients who complete the treatment period should have a Follow-Up Visit 28 days after Visit 23.

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 will not be conducted.

A Follow-Up Visit should be conducted within 28 days of 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 5.3.6. 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 early intervention in patients with attenuated psychosis syndrome. All patients will be treated for 52 weeks.

The primary objective of the statistical analysis is to determine whether BI 409306 significantly increases the likelihood of remission from APS in comparison to placebo. The Cox proportional hazards model, stratified by the baseline use of antipsychotic medication, will be used to estimate and test the hazard ratio of BI 409306 vs. placebo.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The hypotheses for the superiority testing of the primary endpoint are (HR = hazard ratio):

$$H_o: HR_{BI\ 409306\ /\ placebo} = 1 \qquad \text{vs.} \qquad H_a: HR_{BI\ 409306\ /\ placebo} \neq 1$$

Superiority will be declared if the hazard ratio between BI 409306 vs. placebo is significantly greater than 1 at the two-sided type I error level $\alpha = 0.10$.

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 who have analysable data (observed or imputed) in at least one efficacy endpoint

Two follow-up periods are defined:

- Full follow-up: 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 known vital status
- On-treatment: until the date of discontinuation of trial medication + 7 days

Patients will be analysed using actual treatment taken.

7.3.1 Primary endpoint analyses

The primary endpoint is the time to remission from APS as defined in Section 5.1.1.

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 10% significance level. The model includes the treatment effect and NAPLS risk score as covariates and is stratified by baseline use of antipsychotic medication. 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 90% Wald confidence interval. A hazard ratio of more than one favors BI 409306. The analysis will be implemented using [redacted]® PROC PHREG. Cox proportional hazard model assumptions will be verified.

The primary analysis will be performed on the FAS for the on treatment period. The date of remission will be the visit date on which the patient taking the assessment meets the remission criteria. The time to remission is defined to be the start of treatment until remission is achieved. Although patients who discontinue study medication will be followed until the end of the trial for the primary endpoint, the data collected after treatment discontinuation will only be used for a sensitivity analysis. Patients who are lost-to-follow up will be censored for the primary endpoint at the time of their last known SOPS assessment. Patients who begin taking a new prescription or increase in dose of ongoing antipsychotics will be considered as not eligible for remission. Such patients will be censored at the start of new prescription or increase of dose of ongoing antipsychotics. Further details regarding these analyses will be included in the TSAP.

The following sensitivity analyses will be performed: (1) on the primary endpoint that includes only patients from the TS during the time of the full follow-up period and (2) excluding patients who were recruited from the enriched population prior to amendment 3.

Subgroup analyses are planned and will be pre-specified in the TSAP.

7.3.2 Secondary endpoint analyses

Time to event endpoints will be analysed using Cox proportional hazard model as described for the primary endpoint analysis. All change from baseline endpoints specified in Section 5.1.2 will be analysed using the restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM). The model will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, and NAPLS risk score strata, and baseline use of antipsychotic medication, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction. The unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, compound symmetry covariance structure might be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Analyses will be implemented using [redacted]® PROC MIXED. The primary treatment comparisons will be between the placebo and BI 409306 with respect to the mean change from baseline. Adjusted mean change from baseline as well as treatment contrasts will be presented together with the 95% confidence intervals.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 7 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis. 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., by 'treatment at onset'). To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

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

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

Descriptive statistics are planned to quantify the frequency of patients with suicidal ideation and behaviour as recorded on the C-SSRS at any post-baseline visit.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Pharmacogenetic analyses of gene variations within genes associated with the disease and NMDA-R signaling will be carried out using an explorative approach to test the potential influence on therapy response. Analyses may not be carried out if treatment response could not be shown.

7.4 INTERIM ANALYSES

Once there is a sufficient amount of data collected for review, the DMC will hold meetings three times per year. Analyses will be conducted to ensure there is no imbalance in safety endpoints. One formal unblinded interim analysis will be conducted by the DMC when approximately 67% of events have occurred to consider ending the trial early for overwhelming efficacy. Further details on alpha spending will be detailed in the DMC Charter and TSAP.

A blinded sample size reassessment interim analysis with the option to adjust the sample size will be performed by the Sponsor's Trial Statistician when 90% of patients have been randomised or at the same time as the formal interim analysis (whichever happens earlier). The number of observed remissions will be compared to the number predicted. If the actual number is lower than predicted (given the actual already documented study time of randomised patients at the scheduled post-baseline SOPS visits; prediction: 40% for placebo & 57% for BI 409306 at 52 weeks), the sample size may be increased to allow the trial to achieve full power up to a maximum sample size of 400 patients.

7.5 HANDLING OF MISSING DATA

All patients who have not achieved remission will be censored in the analysis of the primary endpoint at the time of last known SOPS assessment. No missing data will be imputed for

the primary and secondary analyses. For secondary endpoints, the statistical model using MMRM will handle missing databased on a likelihood method under the "missing at random" assumption. All FAS patients can be included in the model and therefore participate in variance estimation.

For the SCoRS, if an individual item is missing, it should be imputed with the average of the patient's non-missing item scores. If >5 responses of the 20 items are missing, the composite score of SCoRS will be missing.

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. Approximately equal numbers of patients will be randomised to each treatment group. The randomisation will be stratified by baseline use of antipsychotic medication. 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 CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

Remission rate of the population diagnosed with APS and without intervention was assumed to be 40% (R16-0991) by 52 weeks. The rate of remission for BI 409306 was assumed to be 57% by 52 weeks. This will lead to a hazard ratio of 1.652.
Other study considerations are:

- Two-sided alpha = 0.10
- Dropout = 20% after one year
- Interim analysis checking for early efficacy using user-defined alpha-spending boundary of 0.01 at the 67% information point

Table. 7.7: 1 Power calculations for sample size (for both arms combined) of 300 for various remission rates for BI 409306 with fixed placebo group aggregate first remission rate prediction of 40% by 52 weeks

Remission Rate for Placebo	Remission Rate for BI 409306	Hazard Ratio	Risk Ratio	Power for N=300	# Events needed in total
40%	52%	1.437	1.300	64.9%	126
40%	55%	1.563	1.375	81.5%	130
40%	57%	1.652	1.425	89.3%	133
40%	59%	1.745	1.475	94.4%	136
40%	61%	1.843	1.525	97.4%	139

Table 7.7: 1 displays the power achieved for 300 total randomized patients given a group aggregate first remission rate of 40% for placebo with two-sided α= 0.10 and a user-defined

alpha spending boundary at interim analysis of α=0.01 (two-sided). Group remission rates for BI 409306 treatment of 52%, 55%, 57%, 59% and 61% are considered. Total number of events needed to achieve the power reported is also shown.

Given remission rates of 40% for patients treated with placebo and 57% for patients treated with BI 409306, the risk ratio is 1.425 (implying that patients treated with BI 409306 will have 42.5% more chance of achieving remission of APS compared to placebo).A sample size of 300 (or 150 per group) was selected as the most logical for establishing proof of concept based on the risk / benefit considerations noted above. In addition this was the sample size used in the previous protocol and is kept the same. This translates to 89% power. The type I error was selected to be 10% since this is a phase II study meant to provide an understanding of the effectiveness of the drug without being too strict as in a confirmatory setting.

One hundred and thirty three (133) events (remissions) are needed to be observed to meet the trial objectives. This will not be an event driven trial, so the trial will end when all randomised patients have reached 12 months exposure, regardless of number of remissions observed. However, a blinded sample size assessment will be performed (see Section 7.4) that may allow for an increase in sample size in an attempt to observe the number of remissions necessary for full power.

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

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

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, 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, and also 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 (Investigator Site File).

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/assent 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/assent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent/assent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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/assent form after confirming that the patient understands the contents.

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, 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/assent documentation of this clinical trial.

8.3 RECORDS

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

8.3.1 Source documents

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. In this case the Investigator must make three documented attempts to retrieve previous medical records prior to randomising a patient. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor 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 to ensure patient confidentiality.

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, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient signed informed consent/assent)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history

- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results 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 on-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 on-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). The CRA and auditor may review all CRFs and informed consents/assents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site:
The trial site must retain the source and essential documents (including ISF) according to the national or local requirements (whichever is longer) valid at the time of the end of the trial.
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 regulatory reporting obligation and in accordance with regulatory requirements defined in this CTP. Psychosis events are considered outcome events and are not to be reported as SAEs, unless if considered related to trial medication. See Section 5.3.6.3.

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 and in Section 5.5.1. 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 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.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.

The end of the trial is defined as the date of the last safety follow up visit of the last patient in the whole trial ("Last Patient Out"). The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

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

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

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

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

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

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10. APPENDICES

10.1 BIOMARKER SUB-STUDY: EEG

10.1.1 Flowchart

MAIN STUDY	Trial Periods	Screening Period	Randomised Treatment Period			Follow-up Period
	Visit	**1**	**2**	**3-22**	**EOT**	**F/U**
	Study Week	**-4**	**0**	**1-48**	**52**	**56**
	Study Day	**-28 to -7**	**1**	**8-337**	**365**	**393**
SUB-STUDY	**Sub-study Visit**	**Screening**	**Pre***		**Post**	
	Sub-study Informed Consent/Assent	X				
	EEG (Resting, ERPs)		X		X	

* EEG procedure to be completed before first dosing. Time point also referenced to as the baseline EEG assessment or baseline EEG measurement.

10.1.2 Background and Objectives

10.1.2.1 Background of Biomarker sub-study: EEG

Prediction of psychosis is currently almost exclusively based on clinical criteria. A preventive intervention will benefit from a non-biased, reliable and valid biological biomarker of risk. Recent studies have demonstrated that electroencephalography (EEG)-based biomarkers, including clinical and quantitative EEG [R16-5225, R16-5226, R16-3193] event-related potentials (ERP) [R15-3300, R15-3327, R16-5260], are helpful for predicting later conversion to psychosis in CHR individuals. Thus, with further refinement, these EEG-based measures may eventually provide the clinician with a practical and useful tool for risk classification.

EEG is a non-invasive method to measure the electrical activity of large, synchronously firing, populations of neurons in the brain with electrodes placed on the scalp. Some EEG studies support the validity of quantitative EEG [R16-5226, R16-3193] for prediction of psychosis in the CHR syndrome, including frequency-specific measures of EEG power and cross-site neural synchrony. However, most EEG-based studies of CHR individuals to date have examined ERP components. ERPs are assessed by measuring EEG responses to repetitive auditory, visual or tactile stimuli and are used to probe sensory, perceptual, and cognitive processing with millisecond precision. This high temporal resolution lends itself well to the study of the earliest stages of information processing and the subsequent

transitions from sensory-based perceptual processing to the higher cognitive functions [R15-5841]. ERPs have been widely used to examine basic neuronal activity in both normal brain function and in schizophrenia, and several ERP components have shown promise as potential biomarkers of schizophrenia [R14-3417], including the auditory mismatch negativity and the auditory and visual P300. Accordingly, these components have been most often investigated as predictors of psychosis onset in the CHR syndrome.

Mismatch Negativity

Mismatch negativity (MMN) is a negative voltage ERP component that is elicited following presentation of infrequent physically deviant sounds imbedded in a series of repeated standard sounds [R14-4683, R15-3300]. MMN is elicited automatically, with no overt behavioral response required and with minimal influence of attention. It reflects automatic feature analysis in the auditory cortex, referred to as auditory sensory "echoic" memory because of its dependence on representations of what is "standard" in order to detect deviance in the auditory stream. Deviance in any number of physical sound properties (e.g., pitch, duration, intensity) can elicit variants of MMN, each produced at least partially by distinct neural generators located in primary and secondary auditory cortices as well as bilateral dorsolateral prefrontal cortices [R17-1764]. Deficits in MMN amplitude have been repeatedly demonstrated in patients with schizophrenia [R15-3299]. These deficits and have been linked to negative symptoms and poor functional outcomes. While MMN deficits may improve (but do not normalize) as patients transition from acute to more stable clinical states, they are quite stable in chronic patients (ICCs ~0.90 over 1-2 year test-retest interval), and are not affected by antipsychotic medication [R14-4685; P10-00647]. Additional evidence suggests that MMN is dependent on neurotransmission at NMDA-receptors hypofunction of which has been implicated in schizophrenia [R15-3336; R14-4685]. Recent theoretical perspectives on MMN emphasize its reflection of short-term neural plasticity in the auditory cortex [R10-5103], with repetitions of the standard tone generating an increasingly strong memory trace in the service of auditory predictive coding. In this view, the MMN is a prediction error signal that is elicited when a deviant sound violates the prediction generated by the repeated standard tone. To date, several studies have shown reduced MMN amplitude to predict conversion to psychosis in CHR individuals [R15-3300, R15-3327].

P300 (P3)

The P3 component of the ERP is a positive voltage deflection elicited about 300 ms following the presentation of an infrequent salient "oddball" stimulus randomly imbedded in a series of standard stimuli, usually in the context of an "oddball" target detection task. P3 can be elicited by stimuli presented in any sensory modality, but most commonly has been assessed in auditory or visual oddball tasks. Prevailing views of the P3 consider its amplitude to be a neural reflection of attentional resource allocation [R16-3191]. Its latency is a reflection of processing speed or efficiency during stimulus evaluation [R17-1763]. Two variants of P3, "P3b" and "P3a", have been distinguished based on the nature of the eliciting stimulus, scalp topography, peak latency, and underlying neural generators.

P3b is elicited effort fully by "top down" allocation of attention to infrequent *task relevant* target stimuli requiring a behavioral response (e.g., counting or button press). It has a midline parietal scalp maximum and peaks about 300 ms following the target stimulus [R16-3191]. P3a is elicited automatically by "bottom-up" orienting of attention to infrequent *task*

irrelevant novel or salient stimuli to which no response is required, such as novel sounds or visual images. It has a midline frontocentral scalp maximum and peaks about 20 to 50 ms earlier than P3b.

P3b amplitude reduction and latency delay in auditory oddball tasks is one of the most consistently replicated functional brain abnormalities reported in schizophrenia [R17-1765]. P3b abnormalities in schizophrenia are more robustly observed in auditory than visual paradigms. Importantly, auditory P3b deficits have been shown in first-episode schizophrenia patients as well as in unaffected first-degree relatives of schizophrenic patients [P15-03385]. P3b has also been shown to have some sensitivity to clinical state fluctuations in patients, yet it does not normalize, consistent with its being a trait-like deficit in schizophrenia [R14-3433]. Relatively few studies have examined automatic P3a responses to novel or salient task irrelevant stimuli in schizophrenia. Most of these studies show auditory and/or visual P3a amplitude reductions in schizophrenia in response to novel stimuli [R17-1758].

Previous studies have reported lower auditory P3a [R16-5228, R16-5229, R16-5227, R16-5260] and P3b [R15-3342, R16-1603, R15-3276] amplitudes in CHR patients compared to healthy volunteers and at least one published report [R16-5260] found reduced amplitude of the auditory target P3b to predict conversion to psychosis in CHR individuals.

Gamma Auditory Steady State Response (ASSR)

Synchronization of neural oscillations in the gamma range (30-80 Hz) is considered to be a mechanism for integrating sensory information across different modalities and cortical areas, thereby creating a coherent cortical representation of complex external sensory stimuli. Synchronous gamma oscillations have been shown to contribute to sensory registration and perceptual processes, as well as higher order cognitive operations such as attention and expectation [R17-1761]. The auditory gamma band response is a 40 Hz sinusoidal oscillation that occurs in the first 100 ms following a sound, as measured in vivo using EEG or magneto-encephalography (MEG) [R17-1760]. When an auditory stimulus is repeated at a fixed rate or frequency, it drives the auditory steady-state response (ASSR) in EEG/MEG at the same rate [R17-1756]. Although higher and lower frequencies have been tested, the ASSR reaches a maximum at a 40 Hz repetition rate.

The 40 Hz ASSR has been of particular interest in schizophrenia research because of the dependence of gamma band oscillations on neurotransmitter receptors implicated in the illness, particularly gamma-aminobutryic acid ($GABA_A$) [R15-3342] and glutamatergic N-methyl-D-aspartate (NMDA) receptors [R17-1759]. In particular, fast-spiking parvalbumin-expressing inhibitory GABAergic interneurons have been implicated in the mediation of gamma oscillatory activity. The inhibition of pyramidal cell and interneuron networks by GABAergic interneurons produces gamma band oscillations through an inhibition and rebound excitation cycle that is modulated by $GABA_A$ receptors. Moreover, glutamatergic neurotransmission at NMDA receptors provides excitatory regulation of parvalbumin fast-spiking interneurons, contributing to the generation of gamma oscillations in pyramidal cell networks.

Selective deficits in 40 Hz ASSR in schizophrenia were first reported by Kwon et al [R15-3332]. Subsequent ASSR studies have replicated this reduced 40 Hz ASSR deficit in schizophrenia [R17-1757]. Interestingly, recent studies have further shown that whereas the

power and phase synchrony of the 40 Hz ASSR response is reduced in schizophrenia, EEG gamma power is increased during the inter-trial intervals of this paradigm in schizophrenia patients, and this increase in baseline gamma power is inversely correlated with the power and phase synchrony of the 40 Hz ASSR [R17-1755]. Deficits in 40 Hz ASSR have also been reported in the first-degree relatives of schizophrenia patients [R17-1761], suggesting that abnormal gamma oscillations in response to auditory stimuli may be an endophenotypic marker of genetic risk for the illness. To date, no published reports have examined the 40 Hz ASSR in CHR individuals. However, in unpublished preliminary analyses of data from the NAPLS2 study, CHR individuals showed an increase in baseline gamma EEG power similar and a trend toward reduced 40 Hz ASSR phase synchrony, similar to what has been reported in schizophrenia. While no studies to date have shown the 40 Hz ASSR to predict conversion to psychosis in CHR individuals, it will be included in the current EEG sub-study because of its theoretical sensitivity to glutamatergic NMDA receptor neurotransmission and its translational utility for linking human and animal studies of gamma oscillations.

Given the established links between the amplitude of selected ERP components, the glutamatergic system, schizophrenia, and the transition to psychosis, we will assess quantitative EEG (qEEG) during rest, auditory MMN, auditory and visual P3, and gamma oscillations (baseline gamma power and 40 Hz ASSR power and phase synchrony) at baseline and after 52 weeks of PDE9 inhibition. In order to compare data from the current EEG sub-study with the EEG/ERP data collected from large samples of CHR individuals (n=456) and healthy controls (n=236) in the NAPLS2 study, we use the NAPLS2 EEG paradigms in the current study.

10.1.2.2 Objectives of Biomarker Sub-study: EEG

The objective of this sub-study is to measure and analyze the change of neurophysiological functions of the brain from baseline to the end of treatment in a subset of patients from the main study, which is conducted in individuals with the psychosis-risk syndrome who are treated with BI 409306 50 mg b.i.d. or placebo over a treatment period of 52 weeks.

The study will investigate the clinical utility of resting qEEG, auditory MMN, auditory and visual P3, 40 Hz ASSR power and phase-synchrony, and baseline EEG gamma power (from inter-trial intervals of ASSR paradigm), as biomarkers for risk stratification and targeted intervention. The examination of EEG and ERP measures will be exploratory in nature, potentially providing further insights into the methodologies themselves, neurophysiological changes in patients with the psychosis-risk syndrome, and the effects of the treatment on these measures.

10.1.3 Selection of Study Population

This sub-study will enroll up to 80 patients from a subset of sites participating in the 1289-0032 study, for exploratory purposes.

10.1.3.1 Inclusion Criteria

1. Patients who have provided informed consent/assent to participate in main 1289-0032 study and a separate informed consent/assent for the sub-study before randomisation into the main study, i.e. Visit 2.
2. Patients willing and able to comply with the requirement for EEG procedures.

10.1.3.2 Exclusion Criteria

1. Patients in any clinical/non-clinical circumstance that would interfere with EEG procedures required for this sub-study, based on investigator's discretion (e.g. clinically significant uncompensated hearing loss or severely impaired vision).

10.1.4 Sub-study Design

Resting state EEG, auditory and visual ERP measures, baseline EEG gamma power and 40 Hz ASSR power and phase synchrony measures, will be explored and evaluated at the baseline Visit 2 (pre-dose) and EOT from a subset of the main study patient population.

10.1.5 Methods and Testing procedure

Total EEG testing procedure is expected to last for approximately 90 minutes, including preparing the patient (30 min) and EEG assessments (60 min), but the total duration of EEG set up might vary depending on each investigational site's practice.

Patients will be assessed on the following EEG paradigms: resting state EEG (6 minutes), MMN/Visual Oddball Task, Auditory Oddball Task, 40 Hz ASSR. EEG data will be continuously recorded at a digitization rate of 400 Hz)) from a 32-channel electrode cap with electrodes positioned according to the International 10-20 system, as well as from electrodes placed at each mastoid and at the tip of the nose. Recordings will be referenced to the left mastoid electrode during acquisition, with subsequent re-referencing to linked-mastoids or to the nose tip electrode offline. Vertical and horizontal electro-oculograms, recorded from electrodes above and below the left eye and at the outer canthi of both eyes, respectively, will be used to correct EEG for eye movement and blink artifacts.

Resting State EEG (qEEG):
EEG will be recorded during the resting state for 3 minutes with eyes open and 3 minutes with eyes closed. Quantitative EEG (qEEG) is the mathematical processing of digitally recorded resting state EEG in order to transform the EEG into a format that elucidates relevant information [R15-5841] to allow the identification of CNS pharmacodynamic effects of compounds on spectral power frequency bands. Delta, Theta, Alpha, Beta and Gamma power will be measured at resting state according to the latest IPEG recommendations [International Pharmaco-EEG Society] [R15-5839].

An important application of qEEG is also its use in detecting drug-induced EEG changes occurring early in the course of a treatment, to identify early predictors of clinical response

[R16-5259]. qEEG in this project will be used to assess changes at baseline in patients with attenuated psychosis syndrome compared to end of treatment and to assess the pharmacodynamic response of the brain (i.e. change in power spectra) after multiple doses of BI 409306.

Auditory MMN + Visual Oddball Task:
Auditory MMN is considered largely pre-attentive, and therefore, it is typical to ask patients to ignore the auditory stimuli while engaging their attention towards a visual task. One of the innovations of the NAPLS2 MMN paradigm is that runs concurrently with the Visual Oddball target detection task used to elicit the visual P3 ERP components. Because the auditory tones presented in the MMN paradigm and the visual stimuli presented in the Visual Oddball task are not synchronized, it is possible to through signal averaging to derive from the continuous EEG both the auditory ERPs containing the MMN and the visual ERPs containing the visual P3. Accordingly, the two paradigms are described separately here, but they are presented to the patient simultaneously.

MMN Paradigm: The multi-deviant MMN paradigm involves presentation, in a pseudorandom order, frequent (85% probability) standard tones (633 Hz, 50 ms duration), and three deviants: infrequent (5%) pitch deviant (1000 Hz, 50 ms duration), infrequent (5%) duration deviant tones (633 Hz, 100 ms duration), and infrequent (5%) pitch+duration double deviant tones (1000 Hz, 100 ms duration). All tones have 5 millisecond rise/fall times and are presented via ear phones at 80 dB SPL, with a stimulus-onset asynchrony of 500 ms. Conventional ERP averaging of standards and each deviant type will be generated. ERP data will then be low-pass filtered at 20 Hz and baseline corrected prior to generating deviant-standard difference waves, allowing identification and peak amplitude measurements of pitch-deviant, duration-deviant, and double-deviant MMN.

Visual Oddball Paradigm: The visual oddball task runs concurrently with the auditory MMN paradigm. In the visual oddball task, frequent (80% probability) standard stimuli (small blue circle on white screen), infrequent (10%) target stimuli (large blue circle on a white screen) and infrequent (10%) novel stimuli (fractal images) are presented on a computer screen in a pseudo-random sequence. All images are presented for 500 ms with jittered (1550 ms - 2500 ms) with mean stimulus-onset asynchrony of 2 seconds. Patients are instructed to press a response button with their dominant hand index finger each time a target stimulus appears. A one-minute instructional cartoon is shown before the first run. Conventional ERP averaging of standards, targets, and novels, will be generated. ERP data will then be low-pass filtered at 20 Hz and baseline corrected prior to generating standard, target, and novel ERP waveforms. P3 peak amplitudes are identified between 230 and 550 ms in target (P3b) and novel (P3a) ERP waveforms, and have scalp maxima at midline parietal (Pz) and midline vertex (Cz) electrodes, respectively. In addition, early visual sensory evoked potential components including the visual P1 (between 50-150 ms) will be identified and measured in response to the standard stimuli to assess early visual processing.

The MMN/Visual Oddball paradigm is presented in three runs of about 5 minutes each. Each run comprises 120 standard, 15 target, and 15 novel stimuli. Including instructions, clarification, and run time, the task takes about 20 minutes to complete.

Auditory Oddball Task:
In the auditory oddball task, frequent (80% probability) standard tones (50 ms duration 500 Hz pure tones, 5 ms rise/fall time), infrequent (10%) target tones (50 ms duration 1000 Hz pure tones, 5 ms rise/fall time) and infrequent (10%) novel sounds (durations varying between 250 and 500 ms, variable rise and fall times) are presented via ear phones at 80 dB SPL in a pseudorandom sequence with a fixed stimulus-onset asynchrony of 1250 ms. Patients are instructed to maintain fixation on visual fixation cross on the computer screen and to press a response button with the index finger of their dominant hand each time a target tone is presented. Three runs of the task are presented, each comprising 120 standard tones, 15 target tones and 15 novel sounds. A one-minute instructional cartoon is shown before the first run. Conventional ERP averaging of standards, targets, and novels, will be generated. ERP data will then be low-pass filtered at 20 Hz and baseline corrected prior to generating standard, target, and novel ERP waveforms. P3 peak amplitudes are identified between 230 and 450 ms in target (P3b) and novel (P3a) ERP waveforms, and have scalp maxima at midline parietal (Pz) and midline vertex (Cz) electrodes, respectively. In addition, early auditory sensory evoked potential components including the auditory N1 (between 75-150 ms) will be identified and measured in response to the standard tones to assess early auditory processing. Including instructions, clarification, and run time, the task takes about 15 minutes to complete.

Auditory Steady State Response (ASSR) Paradigm:
ASSR auditory stimuli consist of click trains that drive the auditory cortex at frequencies of 20, 30, or 40 Hz, each presented in a separate block comprising 150 click trains. Clicks are presented at 80 dB via ear phones. Each click train is 500 ms in duration and comprises a series of repeated broadband clicks (1ms duration). For the 20 Hz block, click trains comprise 10 clicks spaced 50 ms apart. For the 30 Hz block, click trains comprise 15 clicks spaced 33.33 ms apart. For the 40 Hz block, click trains comprise 20 clicks spaced 25 ms apart. The stimulus onset asynchrony is fixed at 1100 ms between each click train. ASSR 20 Hz, 30 Hz, and 40 Hz blocks are presented in a pseudo-random order across patients but the same order is maintained within patients across baseline and end of trial assessments. Patients are simply instructed to maintain fixation on visual fixation cross on the computer screen and to passively listen to the auditory stimuli presented. Including instructions, clarification, and run time, the task takes about 10 minutes to complete.

10.1.6 Endpoint

Neurophysiological changes from baseline in qEEG, peak amplitudes (and latencies) of MMN, auditory and visual target P3b and novelty P3a, auditory N1 and visual P1, ASSR total power and ITC (inter-trial phase coherence) for 20, 30, and 40 Hz driving conditions, and baseline gamma power assessed during the ASSR paradigm, will be investigated and their differences between groups will also be investigated.

10.1.8 Statistical Considerations

10.1.8.1 Stastistical Design – Model

An exploratory analysis will be conducted on EEG signals across electrodes and temporal windows to examine drug effects on EEG variables.

10.1.8.2 Null and Alternative Hypotheses

It is not planned to test any statistical hypotheses with regard to any of the endpoints of this EEG sub-study in a confirmatory sense. For the evaluation, a two-sided 95% confidence interval (CI) of adjusted treatment differences will be computed. However, the CI will have to be interpreted in the perspective of the exploratory character of the sub-study, i.e. as an interval estimate for effects under these conditions.

10.1.8.3 Planned Analyses

The statistical model used for the analysis of the EEG endpoints will be an ANOVA (analysis of variance) model. This model will include effects for treatment, age and possibly other effects that will be specified in detail in the TSAP. Further descriptive statistics, including boxplots, will be provided. The variables may be transformed onto a logarithmic scale if severe skewedness is present. More details will be described in the TSAP.

Correlational analyses with clinical endpoints may be made and details therefore will be described in the TSAP.

10.2 OCULAR SAFETY SUB-STUDY

10.2.1 Flowchart

MAIN STUDY	Trial Periods	Screening Period	Randomised Treatment Period			Follow-up Period
	Visit	**1**	**2**	**14**	**EOT**	**F/U**
	Study Week	**-4**	**0**	**24**	**52**	**56**
	Study Day	**-28 to -7**	**1**	**169**	**365**	**393**
SUB-STUDY	**Sub-study Visit**	**Screening**	**Pre***	**6 months**	**12 months**	
	Best Corrected Visual Acuity (BCVA)		X	X	X	
	Color Vision Test (F-M 100)		X	X	X	

* Ocular tests to be completed before first dose.

10.2.2 Background and Objective

In Phase I and II studies with BI 409306, the most frequently observed AEs were eye disorders. All of these AEs have been non-serious and mild to moderate in severity. These events have generally been reported as transient and resolve upon treatment discontinuation. While the frequency of these AEs generally increases with dose, at higher doses there is no obvious relationship between dose and maximum duration and intensity. Onset and duration of these events seem related to Cmax (i.e. in general, onset is approximately within the first 1-2 hours of administration and duration is approximately 30 to 120 minutes). However, first onset after dosing appears variable, with some subjects experiencing these events after first dosing and others only after subsequent dosing. There are no obvious differences in frequency of these events for elderly or CYP2C19 poor metabolizer subjects, but relevant data is limited [c01694347-08].

The objective of this sub-study is to further characterize the ocular safety of BI 409306 in a subset of patients from the main study.

10.2.3 Selection of Study Population

This sub-study will enroll approximately 50 patients from a subset of sites in the United States participating in the main study. Patients enrolled at the participating ocular sub-study sites will be required to complete all of the ocular safety assessments.

10.2.4 Sub-study Design

Best Corrected Visual Acuity and color vision will be evaluated at the baseline Visit 2 (pre-dose), 24 weeks and 52 weeks or EOT from a subset of the main study patient population.

10.2.5 Methods and Testing procedure

Testing conditions (i.e. exam room, chart distance, lighting conditions) should remain constant for each ocular testing visit. Patients who wear eye glasses or contact lenses should wear them for each of the visual acuity and color vision assessments.

Best Corrected Visual Acuity (BCVA)

BCVA will be determined using a Snellen chart at a 10 foot testing distance under standard lighting conditions.

Patients will be instructed to begin at the top of the Snellen chart and read down the chart until they reach a row where all letters on a line cannot be read correctly. The smallest line that a subject can read correctly at the 10 foot distance will be recorded.

BCVA will be determined and recorded at Visit 2 (pre-dose), 24 weeks and 52 weeks or EOT.

Farnsworth-Munsell 100 hue test (F-M 100)

Color vision testing using the Farnsworth-Munsell 100 hue test will be used to evaluate color vision or color vision deficiency. It consists of 93 colors mounted in plastic caps of incremental hue variations, housed in four separate cases. Two caps are fixed as pilot colors at either end of the panel in each case. Patients will be asked to place the color caps in order of hue between each of the fixed anchors. The final arrangement of the hue caps represents the aptitude of the visual system in discerning differences in color hue.

The standard software application included in the F-M 100 package will be used for scoring and analyzing the results. Total error score (TES) will be used as a measurement of color vision. Total error score and level of color vision deficiency classification (e.g. superior, average, low discrimination) will be recorded on the eCRF.

Examination of color vision will be performed at Visit 2 (pre-dose), 24 weeks and 52 weeks or EOT.

10.2.6 Endpoint

Ocular safety will be assessed in a descriptive way based on change from baseline for the following endpoints:

- Best Corrected Visual Acuity test (BCVA) determined using a Snellen Chart
- Total error score from the Farnsworth-Munsel 100 hue testing (F-M 100)

[redacted]

[redacted]

10.2.8 Statistical Considerations

Descriptive statistics for change from baseline will be presented. The descriptive statistics will include paired t-tests and confidence intervals.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		25 May 2017
EudraCT number		2016-004973-42
BI Trial number		1289-0032
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 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title page
Description of change		Revised Lay Title This study tests whether BI 409306 prevents patients with a specific type of mental illness (attenuated psychosis syndrome) from becoming worse. This study looks at how well patients tolerate the medicine and how ~~safe and~~ effective it is over 1 year.
Rationale for change		Removing “safe” from lay title as this could imply that it is not known whether BI 409306 is safe to use.
Sections to be changed		Synopsis Section 4.2.1 Section 5.1.1 Section 7.3.1

Description of change		Clarification of psychosis/outcome event Synopsis First episode of psychosis defined as: One or more of the following Positive Symptoms (Scale of Prodromal Symptoms (SOPS) criteria) in the psychotic range (rated at level 6): • Unusual Thought Content/Delusional Ideas • Suspiciousness/Persecutory Ideas • Grandiosity • Perceptual Abnormalities/Hallucinations • Disorganized Communication AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month. OR A new prescription or increase in dose of an ongoing antipsychotic medication ~~for worsening of psychosis symptoms.~~ Section 4.2.1 When a patient begins a new prescription or increases their dose of an ongoing antipsychotic medication ~~due to worsening of psychosis symptoms~~, this is an outcome event. The available information (e.g., SOPS interview video, medical records from prescribing physician) will be subsequently ~~adjudicated~~ reviewed by the Central Rating Committee ~~to determine whether the patient has converted to psychosis.~~ Section 7.3.1 The following sensitivity analyses will be performed: (1) on the primary endpoint that includes only patients from the TS during the time of the on-treatment follow-up period and (2) on the portion of the primary endpoint derived from the SOPS (that is, excluding patients with new prescriptions or increases in dose of ongoing antipsychotic medication ~~for worsening of psychosis symptoms~~).

Rationale for change		Clarify that psychosis/outcome event criteria are met when a patient receives a new prescription or increase in dose of antipsychotic medication.
Section to be changed		Flow Chart
Description of change		[redacted]
Rationale for change		
Sections to be changed		Flow Chart (footnote 9) Section 3.3.2 Section 6.2.1 Section 6.2.2
Description of change		Change "Central Rating Committee" to "[redacted]" <u>Flow Chart (footnote 9)</u> 9. The Structured Interview for Psychosis-Risk Syndromes (SIPS) and Scale of Prodromal Symptoms (SOPS) interviews will be video-taped for review by ~~the Central Rating Committee~~ [redacted]. <u>Section 3.3.2</u> 1. Meet diagnostic criteria for attenuated psychosis syndrome as defined in DSM-5 and determined by SIPS administered at screening and diagnosis confirmed by ~~Central Rating Committee~~ [redacted] after review of video-taped SIPS interview. <u>Section 6.2.1</u> If the rater at the site concludes that the patient meets diagnostic criteria for APS and has a qualifying NAPLS risk calculator score, both the video-taped interview and the SIPS response forms must be reviewed and diagnosis confirmed by ~~the Central Rating Committee~~ [redacted] prior to randomisation. <u>Section 6.2.2</u> During the treatment period, all SIPS/SOPS assessments will be video-taped for review by ~~the Central Rating Committee~~ [redacted]

		Section 6.2.2 If any Positive Symptom Score of 6/Severe and Psychotic is assigned while administering the SOPS, the following should occur: • The PI should immediately contact ~~the Central Rating Committee chair/contact~~ [redacted] to arrange for expedited video review.
Rationale for change		Clarification that [redacted] will perform the first review of SIPS/SOPS video recorded interviews.
Section to be changed		Abbreviations
Description of change		Abbreviations added and removed **ASSR/auditory steady-state response** **$GABA_A$/gamma-aminobutryic acid** **ICC/Intra-class correlation coefficient** **ITC/Inter-trial phase coherence** **MEG/magneto-encephalography** ~~BVMT-R/Brief Visuospatial Memory Test – Revised~~ ~~CPT-IP/Continuous Performance Test – Identical Pairs~~ ~~MSCEIT/Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions~~ ~~NAB/Neuropsychological Assessment Battery: Mazes~~ ~~WMS-III/Wechsler Memory Scale-III~~
Rationale for change		Removing abbreviations not referenced in the protocol; new abbreviations added that apply to changes in Section 10.
Section to be changed		Section 3.3.1
Description of change		Patients with APS who have a NAPLS risk calculator score ≥ 0.20 at screening indicative of a group aggregate risk of greater than 35% of conversion to psychosis at 52 weeks will be included. Please refer to the ISF for the NAPLS risk calculator website. **Patients may be enrolled if they are currently taking antipsychotic medication (See Section 4.2.1). If a patient discontinues an antipsychotic medication, they can be randomized two weeks after discontinuation.**

Rationale for change		Clarification for patients taking antipsychotic medication during the screening period.
Section to be changed		Section 3.3.3
Description of change		Exclusion Criteria added/clarified 1. Present or past diagnosis of schizophrenia, schizophreniform, schizoaffective disorder, bipolar disorder I ~~or II~~, major depressive disorder with psychotic features, delusional disorder, brief psychotic disorder, other specified schizophrenia spectrum and other psychotic disorder (except attenuated psychosis syndrome), and unspecified schizophrenia spectrum and other psychotic disorder, according to DSM-5. **2. Patients taking antipsychotic medication for less than 8 weeks prior to informed consent.** **3. Patients who begin taking an antipsychotic between Visit 1 and Visit 2.** **4. Patients who have discontinued an antipsychotic medication less than two weeks prior to randomization.** 10. ~~Diagnosis of a~~ **A** serious developmental disorder **that in the judgement of the investigator would inhibit the patient's ability to comply with all study procedures, or** mental retardation (documented IQ <70), ~~cognitive disorder,~~ or acute attenuated symptoms exclusively related to intoxication from a psychotropic substance.
Rationale for change		Clarification of existing exclusion criteria and additional criteria to define stability of antipsychotic medication.
Section to be changed		Section 4.2.1
Description of change		Antipsychotic medication clarification If a patient is enrolled who is taking an antipsychotic medication **that will continue during the treatment period**, it is extremely important they continue to take the current antipsychotic medication at the same dose as when the patient was randomized. The dose **of an antipsychotic medication** can be decreased or discontinued entirely. A patient's dose of antipsychotic medication should be increased only

		in circumstances of significant worsening of psychosis symptoms **that the investigator feels qualifies for a first episode of psychosis.** ~~Increasing the dose of antipsychotic medication for other reasons will be a protocol violation.~~
Rationale for change		Clarification for patients taking antipsychotic medication during the treatment period.
Section to be changed		Section 4.3
Description of change		Added instruction about monitoring for study drug abuse **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 patient's source and on the appropriate eCRFs.**
Rationale for change		Text added regarding monitoring of potential study drug abuse and/or diversion.
Section to be changed		Section 5.3.2
Description of change		Clarification about vital signs collection **A similar type of** ~~The same calibrated~~ instrument/scale should be used for all measurements. **Vital signs will be measured after the patient has been sitting for 5 minutes.**
Rationale for change		Clarification about the type of instruments that should be used to measure vital signs, and when measurements should be collected.
Section to be changed		Section 5.3.4
Description of change		Clarification about ECG measurement The 12-lead ECGs will be performed as scheduled in the Flow Chart **after 5 minutes in the supine position.**
Rationale for change		Clarify when ECG should be performed.
Section to be changed		Section 5.3.6.2
Description of change		Added explanation about monitoring for abuse related AEs **The potential for study drug abuse-related adverse events will be closely monitored and narratives provided in the CTR. Narratives will include standard AE data collection, including time of onset, duration, severity and outcome.**
Rationale for change		Explanation regarding monitoring of potential abuse related adverse events.

Section to be changed		Section 5.5.2
Description of change		Collection methods for the samples for ~~CYP2C19 genotyping at screening and~~ pre-specified pharmacogenomic analyses at Visit 2 are identical to that of the optional DNA banking sample. Please refer to Section 5.5.1.1. **Detailed instructions on sampling, preparation, processing, shipment and storage of the samples collected at screening for CYP2C19 genotyping are provided in the laboratory manual.**
Rationale for change		Clarification about collection of CYP2C19 genotyping samples.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 7.4
Description of change		Clarification of interim analyses One formal **unblinded** interim analysis will be conducted **by the DMC** when approximately 67% of events have occurred to consider ending the trial early for overwhelming efficacy. A blinded sample size reassessment **interim analysis** with the option to adjust the sample size will be performed by the Sponsor's Trial Statistician when 90% of patients have been randomised or at the same time as the formal interim analysis (whichever happens earlier).
Rationale for change		Clarification of interim analyses
Section to be changed		Section 9
Description of change		The following references were added: **P10-00647** **R10-5103** **R14-4685** **R15-3299** **R15-3332** **R15-3336** **R15-3343** **R16-3191**

		R17-1755 **R17-1756** **R17-1757** **R17-1758** **R17-1759** **R17-1760** **R17-1761** **R17-1763** **R17-1764** **R17-1765**
Rationale for change		References related to EEG added.
Section to be changed		Section 10
Description of change		EEG section revised to provide further background information and EEG paradigms adapted to be compatible with the NAPLS2 EEG paradigms.
Rationale for change		Adapting the NAPLS2 EEG paradigms in the current study in order to compare data from the current EEG sub-study with the EEG/ERP data collected from large samples of CHR individuals and healthy controls in the NAPLS2 study.

Number of global amendment		2
Date of CTP revision		10 Jul 2017
EudraCT number		2016-004973-42
BI Trial number		1289-0032
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 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Flow Chart
Description of change		ECG and safety laboratory tests added at Visits 8, 12, 16, 20 and 22
Rationale for change		Increase frequency of safety monitoring
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria added • Patients with a history of moderate to severe hepatic impairment (Child-Pugh B / C). • Patients with a history of moderate to severe renal impairment (Stage 3 – 5).
Rationale for change		Exclude patients with compromised organ function

Number of global amendment		3
Date of CTP revision		04 Oct 2018
EudraCT number		2016-004973-42
BI Trial number		1289-0032
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 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.
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		**Objective:** To investigate the efficacy, safety and tolerability of BI 409306 compared to placebo given for 52 weeks to patients with attenuated psychosis syndrome. The study is designed to show superiority of BI 409306 over placebo in **achieving remission of APS** ~~preventing first episode of psychosis~~, as well as improvement in cognition and functional capacity.
Rationale for change		To reflect change in primary endpoint.
Section to be changed		Synopsis
Description of change		**Main criteria for inclusion:**

		~~Risk calculator score ≥0.20 (using the North American Prodrome Longitudinal Study (NAPLS) risk calculator) at screening indicative of a group aggregate risk of greater than 35% risk of conversion to psychosis within the next 52 weeks.~~ ~~No present or past diagnosis of schizophrenia, schizophreniform, schizoaffective disorder, bipolar disorder I, major depressive disorder with psychotic features, delusional disorder, brief psychotic disorder, other specified schizophrenia spectrum and other psychotic disorder (except attenuated psychosis syndrome), and unspecified schizophrenia spectrum and other psychotic disorder, according to DSM-5.~~
Rationale for change		To reflect change in primary endpoint.
Section to be changed		Synopsis
Description of change		**Endpoints**: Primary Endpoint: The primary endpoint is **time to remission from APS** ~~time to first episode of psychosis~~ within a 52 week timeframe. **Remission from APS is defined as a score of <3 on all of the P1-P5 Positive Symptom items of the SOPS and maintained until the end of treatment.** ~~First episode of psychosis defined as:~~ ~~One or more of the following Positive Symptoms (Scale of Prodromal Symptoms (SOPS) criteria) in the psychotic range (rated at level 6):~~ • ~~Unusual Thought Content/Delusional Ideas~~ • ~~Suspiciousness/Persecutory Ideas~~ • ~~Grandiosity~~ • ~~Perceptual Abnormalities/Hallucinations~~ • ~~Disorganized Communication~~ ~~AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month.~~ ~~OR~~ ~~A new prescription or increase in dose of an ongoing antipsychotic medication.~~ ~~Time of onset of first episode psychosis is defined using the rater's best estimate as determined in the SOPS interview or when the patient began taking a new prescription or increased the dose of antipsychotic medication.~~

		Secondary Endpoints: • **Time to first episode of psychosis within a 52 week timeframe as adjudicated by the Central Rating Committee. First episode of psychosis defined as one or more SOPS P1-P5 rated a 6 AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month. OR a new prescription or increase in dose of an ongoing antipsychotic medication. Time of onset of first episode psychosis is defined using the rater's best estimate as determined in the SOPS interview or when the patient began taking a new prescription or increased the dose of antipsychotic medication.**
Rationale for change		To reflect changes in primary and secondary endpoints.
Section to be changed		Synopsis
Description of change		**Statistical Methods:** For the primary endpoint of ~~time to first episode of psychosis~~ **remission from APS**, 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 10% significance level. The model includes the treatment effect **and categorized NAPLS risk score** as ~~the only~~ **covariates** and is stratified by ~~NAPLS risk calculator score and~~ baseline use of antipsychotics. **Time to event endpoints will be analysed using Cox proportional hazard model and** change from baseline endpoints will be analysed using the restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM).
Rationale for change		To reflect changes in primary and secondary endpoints.
Section to be changed		Flow Chart
Description of change		Revisions to Rows: ~~Cannabis~~ **Substance** Use Assessment NAPLS Risk Calculator (row moved to lower section of flow chart) Footnotes: ****** The End of Study CRFs will be completed at the time of the Follow-Up Visit for completed patients. Patients who prematurely discontinue study drug and remain in the study will have the End of Study CRFs completed one year after randomization.** **5. Patients will be asked whether they have ever or are currently using/consuming tobacco, alcohol and cannabis.**

		11. The BACS SC and HVLT-R are paper assessments. The paper BACS SC at Visit 23 is a different version than the BACS SC in the BAC App that is also completed at Visit 23. ~~11. The North American Prodromal Longitudinal study (NAPLS) risk calculator uses the following predictor variables: 1. Age, 2. Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS SC), 3. Hopkins Verbal Learning Test (HVLT-R), 4. SIPS items P1 and P2 (unusual thought content and suspiciousness), and 5. Global Functioning: Social (GF:Social).~~ 14. The Columbia Suicide Severity Rating Scale (C-SSRS) Baseline/Screening version will be used at Visit 1 (Screening Visit). At other scheduled visits, the C-SSRS Since Last Visit version will be used. **The screening eC-SSRS report must be reviewed by the investigator/qualified rater for validity prior to randomization.** **21. The NAPLS risk calculator score will be calculated and data entered by [redacted].**
Rationale for change		Revision to Substance Use Assessment to align with CRFs; clarification of the timing End of Study data collection; additional instruction to align with revised suicidal behavior exclusion criterion; moved NAPLS Risk Calculator row lower in flow chart since sites no longer need to calculate the risk score.
Section to be changed		Abbreviations
Description of change		Abbreviations added: **BCVA/ Best Corrected Visual Acuity** **F-M 100/Farnsworth-Munsell 100 hue test** **TES/Total error score**
Rationale for change		New abbreviations added that apply to changes in Section 10.2.
Section to be changed		1. Introduction
Description of change		BI 409306 is a Phosphodiesterase-9 (PDE9) inhibitor under development for the ~~treatment of Alzheimer's disease (AD)~~, **prevention of relapse in persons with** schizophrenia**,** and for the treatment of ~~prevention of first episode of psychosis (FEP) in~~ patients with attenuated psychosis syndrome (APS) 1.1 Medical Background These at-risk individuals represent a population who stand to benefit from early detection and **treatment of the aforementioned symptoms as well as** possible prevention of subsequent psychotic conversion. Such **symptoms as well as the occurrence of** ~~first~~ psychotic episodes are the focus of the investigation plan for BI 409306.

		Data from a recent analysis of a large US insurance claims database (R18-0654) demonstrated that as far back as five years before an incident diagnosis of schizophrenia subjects presented for care and utilized healthcare resources at a rate twice that of age and region matched controls. The data demonstrated that these individuals are prescribed a number of medications including antipsychotics and antidepressants, suggesting that their level of symptomatology has already become problematic in their lives.
Rationale for change		To reflect change in primary endpoint
Section to be changed		2.1 Rationale for Performing the Trial
Description of change		In conclusion, these preclinical and clinical findings suggest that inhibition of PDE9 by BI 409306 represents a rational approach for improvement and potentially normalization of those processes dysfunctional in individuals with attenuated psychosis syndrome, leading to **reduction or remission of the symptoms, and** the delay or even prevention of FEP in individuals with attenuated psychosis syndrome via decreasing synaptic over-pruning and strengthening the NMDA-receptor signaling and synaptic plasticity
Rationale for change		To reflect change in primary endpoint
Section to be changed		2.2 Trial Objectives
Description of change		The objective of this study is to investigate the efficacy, safety and tolerability of BI 409306 compared to placebo given for 52 weeks to patients with attenuated psychosis syndrome. The study is designed to show superiority of BI 409306 over placebo in ~~preventing first episode psychosis~~ **achieving remission of APS** as well as improvement in cognition and functional capacity. **A subset of patients will complete ocular safety tests to further characterize the ocular safety of BI 409306. See Section 10.2.**
Rationale for change		To reflect change in primary endpoint and addition of ocular safety sub-study
Section to be changed		2.3 Benefit Risk Assessment
Description of change		NAPLS has constructed an algorithm to estimate the risk of conversion to psychosis depending on several risk factors. When applied, this algorithm predicts the conversion

		rates for patients without treatment [R16-3564]. ~~In order to minimize exposure to individuals at the lower strata of risk for conversion to psychosis,~~ This algorithm will be utilized to ~~enrich~~ **assess** the sample of eligible patients ~~with those more likely to convert to psychosis within the treatment period than would occur in a naturalistic setting~~ **to better quantify risk for conversion.** Patients who convert to psychosis will continue to be followed in the trial. A potential effect of BI 409306, a centrally acting compound, on suicidality cannot be ruled out. **This must be balanced with an effort to ensure that the population under study is representative to the extent possible, of the population intended to be prescribed the compound, should it ever receive regulatory approval. Since suicidality is known to be common in the CHR population, the exclusion criteria for this study allow for an assessment of past suicidal behaviour by the investigator while excluding recent significant suicidal ideation.** ~~Therefore, s~~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.
Rationale for change		To reflect change in primary endpoint and revised exclusion #6.
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		Randomisation will be stratified by ~~the NAPLS risk score and~~ baseline use of antipsychotics
Rationale for change		To reflect change to inclusion criteria
Section to be changed		3.2 Discussion of Trial Design, Including the Choice of Control Group
Description of change		A randomised, double-blind, parallel group design was chosen for this study to observe the effects of BI 409306 compared to placebo **on the remission of APS symptoms** ~~in the prevention of first episode psychosis~~ as well as improvement in cognition and functional capacity. There is currently no approved medication indicated for **the treatment of symptoms of APS** ~~early intervention~~ or **for** the prevention of first episode of psychosis
Rationale for change		To reflect change to primary endpoint
Section to be changed		3.3 Selection of Trial Population
Description of change		It is planned that approximately 50 trial centres in ~~three~~ **up to four** countries will be participating in this trial to randomise

		300 patients
Rationale for change		To allow for the possibility of another participating country
Section to be changed		3.3.1 Main Diagnosis for trial entry
Description of change		Patients **meeting the following diagnostic criteria for attenuated psychosis syndrome (APS) as defined in DSM-5 will be included:** ~~with APS who have a NAPLS risk calculator score ≥ 0.20 at screening indicative of a group aggregate risk of greater than 35% of conversion to psychosis at 52 weeks will be included.~~ ~~Please refer to the ISF for the NAPLS risk calculator website.~~ **Per DSM-V, the proposed diagnostic criteria for APS are:** **A. At least one of the following of symptoms is present in attenuated form, with relatively intact reality testing and is of sufficient severity or frequency to warrant clinical attention:** • **Delusions** • **Hallucinations** • **Disorganized speech.** **B. Symptom(s) must have been present at least once per week in the last 1 month** **C. Symptom(s) must have begun or worsened in the past year** **D. Symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention** **E. Symptom(s) is not better explained by another mental disorder, including: Depressive or bipolar disorder with psychotic features and is not attributable to physiological effects of a substance or another medical condition** **F. Criteria for any psychotic disorder have never been met.** **A diagnosis of Attenuated Positive Symptom Syndrome is defined by the presence of recent attenuated positive symptoms that meet ALL of 5 criteria: sufficient severity (criterion A), sufficient frequency (criterion B), recency of onset or worsening (criterion C), associated with sufficient distress or disability to warrant clinical attention ("warrant attention criterion," criterion D), and not have been likely due to another disorder ("attribution criterion," criterion E).**
Rationale for change		To reflect change to inclusion criteria.
Section to be changed		3.3.2 Inclusion Criteria

Description of change		~~2. NAPLS risk calculator score ≥ 0.20 at screening.~~ ***Inclusion criterion 2 removed in global amendment 3. Numbering of subsequent criteria not changed.***
Rationale for change		To reflect change in primary endpoint
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Exclusion criterion revised: 2. Patients taking antipsychotic medication for less than 8 weeks ~~prior to informed consent~~ **or patients taking antipsychotic medication for a longer duration but who have not been on a stable dose for 8 weeks prior to informed consent** prior to informed consent. 6.~~ Any~~ Suicidal behavior in the past 2 years ~~(i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)~~ **reported in the Columbia Suicide Severity Rating Scale (C-SSRS) with a lethality of attempt ≥1, or with a lethality of 0 but a potential lethality of 2, or that in the judgement of the investigator would jeopardize the patient's safety while participating in the trial. The investigator/qualified rater must review all screening C-SSRS reports prior to randomization, documenting an additional interview assessing lethality of the behavior history when appropriate.** 14. ~~Significant history of drug or alcohol dependence or abuse~~ **Meets criteria for** Substance Use Disorder ~~as defined in~~(DSM-5) within the ~~last~~ six months prior to informed consent/assent. Exclusion criterion added: **24. Known hypersensitivity to the drug product excipients (lactose monohydrate, pregelatinized starch, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, talc and iron oxide yellow).**
Rationale for change		Clarification of exclusion #2, #6, and 14, and addition of criterion #24 to exclude patients with hypersensitivity to the excipients in the IMP.
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		Premature study drug discontinuation 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 Section 6.2.2. Patients who discontinue study drug prematurely should ideally be observed until the end of the ~~trial~~ **study (week 52)** as if they were still receiving blinded study treatment.
Rationale for change		Clarification to emphasize that patients who prematurely discontinue study drug should be followed for one year after randomization.
Section to be changed		4.2.1 Other treatments and emergency procedures
Description of change		**Patients experiencing a first episode of psychosis should continue taking study drug at the discretion of the investigator.**
Rationale for change		Clarification that patients should remain in the study after experiencing psychosis.
Section to be changed		5.1.1 Primary Endpoint
Description of change		The primary endpoint is **time to remission from APS** ~~time to first episode of psychosis~~ within a 52 week timeframe ~~as adjudicated by the Central Rating Committee~~. **Per DSM-V, the proposed diagnostic criteria for APS are:** **A. At least one of the following of symptoms is present in attenuated form, with relatively intact reality testing and is of sufficient severity or frequency to warrant clinical attention:** • **Delusions** • **Hallucinations** • **Disorganized speech.** **B. Symptom(s) must have been present at least once per week in the last 1 month** **C. Symptom(s) must have begun or worsened in the past year** **D. Symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention** **E. Symptom(s) is not better explained by another mental disorder, including: Depressive or bipolar disorder with psychotic features and is not attributable to physiological effects of a substance or another medical condition** **F. Criteria for any psychotic disorder have never been met.** **A diagnosis of Attenuated Positive Symptom Syndrome is defined by the presence of recent attenuated positive symptoms that meet ALL of 5 criteria: sufficient severity (criterion A), sufficient frequency (criterion B), recency of**

		onset or worsening (criterion C), associated with sufficient distress or disability to warrant clinical attention ("warrant attention criterion," criterion D), and not likely due to another disorder ("attribution criterion," criterion E). **A patient in remission is defined as someone who no longer meets the severity criterion.** **Remission from APS is defined as a score of <3 on all of the P1-P5 Positive Symptom items of the SOPS and maintained until the end of treatment.** ~~One or more of the following Positive Symptoms (Scale of Prodromal Symptoms (SOPS) criteria) in the psychotic range (rated at level 6):~~ ~~• Unusual Thought Content/Delusional Ideas~~ ~~• Suspiciousness/Persecutory Ideas~~ ~~• Grandiosity~~ ~~• Perceptual Abnormalities/Hallucinations~~ ~~• Disorganized Communication~~ ~~AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month.~~ ~~OR~~ ~~A new prescription or increase in dose of an ongoing antipsychotic medication.~~ ~~Time of onset of first episode psychosis is defined using the rater's best estimate as determined in the SOPS interview or when the patient began taking a new prescription or increased the dose of antipsychotic medication.~~
Rationale for change		Change in primary endpoint.
Section to be changed		5.1.2 Secondary Endpoints
Description of change		• **Time to first episode of psychosis within a 52 week timeframe as adjudicated by the Central Rating Committee. First episode of psychosis defined as one or more SOPS P1-P5 rated a 6 AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month. OR a new prescription or increase in dose of an ongoing antipsychotic medication.** **Time of onset of first episode psychosis is defined**

		using the rater's best estimate as determined in the SOPS interview or when the patient began taking a new prescription or increased the dose of antipsychotic medication.
Rationale for change		To reflect change in primary endpoint. Formal primary endpoint now a secondary endpoint.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		5.2 Assessment of Efficacy
Description of change		**Remission of APS,** conversion to psychosis, functional capacity, cognitive function, and disease state will be measured by the batteries and questionnaires listed below: The Positive scale is used to make a diagnosis of attenuated psychosis syndrome **(APS)** and conversion to psychosis. **To meet criteria for APS, a patient must at some point have rated level "3", "4", or "5" on at least one of the P1-P5 Positive Symptom items of the SOPS. The symptom(s) must have occurred at the then-current intensity level at an average frequency of at least once per week in the past month, and must not have been likely due to another disorder**. The **Negative, Disorganization and General** ~~other~~ domains are used to assess the severity of the diagnosis [R15-1441]. A composite T score that ~~averages five~~ **is calculated using the six** of the standardized scaled sub-test scores will be generated. ~~The token motor test score will not be included because at the time of protocol writing there were no norms available on this sub-test.~~
Rationale for change		To reflect change in primary endpoint; to clarify APS diagnosis; update to the calculation of BAC App T score.
Section to be changed		5.3.5.1 Assessment of suicidality
Description of change		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. **The investigator/qualified rater must perform and document an additional interview if there is doubt about the validity of the report.** ~~Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist.~~

Rationale for change		To clarify C-SSRS procedures.
Section to be changed		5.3.6.1 Definitions of AEs
Description of change		~~Adverse reaction~~ ~~An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.~~ **Serious adverse event** A serious adverse event (SAE) is defined as any AE**,** which **fulfils at least one of the following criteria**: • results in death, • is life-threatening, this 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 prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • is a congenital anomaly / birth defect,~~ or~~ is ~~to be~~ deemed serious for any other reason if it is an important medical event when based ~~up~~on appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. ~~Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.~~ 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. ~~Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.~~ **Causal relationship of AEs** ~~The definition of an adverse reaction implies at least a~~

		~~reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.~~ Medical judgment should be used to determine ~~the relationship~~ **whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment**, 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.
Rationale for change		To align this section with updated standard protocol text.
Section to be changed		5.3.6.2 Adverse event collection and reporting
Description of change		**<u>AE Collection</u>** 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).** • From signing the informed consent/assent onwards through the Residual Effect Period (REP), until individual patient's end of trial: -all AEs (serious and non-serious) and all AESIs. ~~However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits include telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial the Investigator must report related SAEs and related AESIs.~~ After the individual patient's end of trial: the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of **by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form, but not on the CRF.** **The rules for Adverse Event Reporting exemptions still apply, please see section 5.3.6.3.** **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 only report relevant SAEs and relevant AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form, but not on the CRF.** **The rules for Adverse Event Reporting exemptions still apply, please see section 5.3.6.3.**
Rationale for change		To align this section with updated standard protocol text.
Section to be changed		6.2.1 Screening Period
Description of change		If the rater at the site concludes that the patient meets diagnostic criteria for APS ~~and has a qualifying NAPLS risk calculator score~~, both the video-taped interview and the SIPS response forms must be reviewed and diagnosis confirmed by [redacted] prior to randomisation. Please refer to the **Assessment Procedures Binder** ~~SIPS Process Document in the ISF~~ for further information.
Rationale for change		To reflect change to inclusion criteria; clarification on the name of the procedural reference.
Section to be changed		6.2.2 Treatment Period
Description of change		Please refer to the **Assessment Procedures Binder** ~~SIPS Process Document in the ISF.~~ **Patients experiencing a first episode of psychosis should continue taking study drug at the discretion of the investigator.**
Rationale for change		Clarification on the name of the procedural reference; clarification that patients should remain in the study after experiencing psychosis.
Section to be changed		7.1 Statistical Design - Model
Description of change		The primary objective of the statistical analysis is to determine whether BI 409306 significantly ~~reduces the risk of first episode of psychosis~~ **increases the likelihood of remission from APS** in comparison to placebo. The Cox proportional hazards model, stratified by ~~the NAPLS risk score strata and~~ baseline use of antipsychotic medication, will be used to

		estimate and test the hazard ratio of BI 409306 vs. placebo. ~~The NAPLS risk score is dichotomized into two strata:~~ ~~• 0.20 ≤ NAPLS risk score < 0.40~~ ~~• NAPLS risk score ≥ 0.40.~~
Rationale for change		To reflect change in primary endpoint.
Section to be changed		7.2 Null and Alternative Hypotheses
Description of change		Superiority will be declared if the hazard ratio between BI 409306 vs. placebo is significantly ~~less~~ **greater** than 1 at the two-sided type I error level $\alpha = 0.10$.
Rationale for change		To reflect change in primary endpoint.
Section to be changed		7.3.1 Primary Endpoint analyses
Description of change		The primary endpoint is the time to ~~first episode psychosis~~ **remission of from APS** as defined in Section 5.1.2. 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 10% significance level. The model includes the treatment effect **and NAPLS risk score** as ~~the only~~ covariates and is stratified by ~~NAPLS risk score and~~ baseline use of antipsychotic medication. A hazard ratio of **more** ~~less~~ than one favors BI 409306. The primary analysis will be performed on the FAS for the ~~full follow-up~~ **on treatment** period. **The date of remission will be the visit date on which the patient taking the assessment meets the remission criteria. The time to remission is defined to be the start of treatment until remission is achieved. Although** ~~P~~patients who discontinue study medication will be followed until the end of the trial for the primary endpoint, **the data collected after treatment discontinuation will be only used for sensitivity analysis.** Patients who are lost-to-follow up will be censored for the primary endpoint at the time of their last known SOPS assessment. Patients who begin taking a new prescription or increase in dose of ongoing antipsychotics will be considered as not eligible for remission. **Such patients will be censored at the start of new prescription or increase of dose of ongoing antipsychotics. Further details regarding these analyses will be included in the TSAP.** The following sensitivity analyses will be performed: (1) on the primary endpoint that includes only patients from the TS during the time of the ~~on-treatment~~ **full** follow-up period and (2) **excluding patients who were recruited from the enriched**

		population prior to amendment 3 ~~on the portion of the primary endpoint derived from the SOPS (that is, excluding patients with new prescriptions or increases in dose of ongoing antipsychotic medication).~~
Rationale for change		To reflect change in primary endpoint.
Section to be changed		7.3.2 Secondary endpoint analyses
Description of change		**Time to event endpoints will be analysed using Cox proportional hazard model as described for the primary endpoint analysis. All change from baseline endpoints specified in Section 5.1.2 will be analysed using the restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM).** ~~All secondary endpoints specified in Section 5.1.2 will be analyzed using a restricted maximum likelihood estimation based on MMRM for the change from baseline.~~
Rationale for change		To reflect change in secondary endpoint.
Section to be changed		7.4 Interim Analyses
Description of change		**Once there is a sufficient amount of data collected for review, t**~~T~~he DMC will hold meetings three times per year. The number of **observed remissions** ~~primary endpoints~~ will be compared to the number predicted. If the actual number is lower than predicted (given the actual already documented study time of randomised patients at the scheduled post-baseline SOPS visits; prediction: ~~35~~ **40**% **for placebo** & ~~20~~ **57**% **for BI 409306** at 52 weeks), the sample size may be increased to allow the trial to achieve full power up to a maximum sample size of 400 patients.
Rationale for change		To reflect change in primary endpoint.
Section to be changed		7.5 Handling of Missing Data
Description of change		All patients who have not ~~converted to psychosis~~ **achieved remission** will be censored in the analysis of the primary endpoint at the time of last known SOPS assessment.
Rationale for change		To reflect change in primary endpoint.
Section to be changed		7.6 Randomization
Description of change		The randomisation will be stratified by ~~risk score on the NAPLS risk calculator (0.20 ≤ score < 0.40 vs. score ≥ 0.40), and~~ baseline use of antipsychotic medication.
Rationale for change		To reflect removal of stratification factor.
Section to be changed		7.7 Determination of Sample Size
Description of change		**Remission rate of the population diagnosed with APS and**

without intervention was assumed to be 40% (Addington, 2011) by 52 weeks. The rate of remission for BI 409306 was assumed to be 57% by 52 weeks. This will lead to a hazard ratio of 1.652 ~~NAPLS has constructed an algorithm to estimate the risk of conversion to first episode psychosis depending on several risk factors. This algorithm, when applied, predicts the conversion rates for patients without treatment, i.e., patients taking placebo. For example, for the group of patients with a risk score ≥ 0.20, approximately 35% of patients are predicted to convert to psychosis within one year. For the group of patients with risk score ≥ 0.15, approximately 27% of patients are predicted to convert to psychosis within one year [R16-3564]. Selection of the targeted conversion rate in the APS population is somewhat arbitrary, but the risk score ≥ 0.20 was selected to maximize the risk of conversion to enable the trial to be able to differentiate between treatment and placebo within an acceptable risk/benefit profile.~~

Table 7.7: 1 **Power calculations for** sample size (for both arms combined) **of 300** for various ~~conversion~~ **remission** rates for BI 409306 with fixed placebo group aggregate ~~conversion~~ **first remission** rate prediction of ~~35%~~**40% by 52 weeks**

	~~BI 409306 group aggregate conversion rate~~		
	~~15%~~	~~20%~~	~~25%~~
~~80% power~~	~~Total N=115 patients~~	~~230~~	~~560~~
~~90% power~~	~~160~~	~~319~~	~~775~~

Remission Rate for Placebo	Remission Rate for BI 409306	Hazard Ratio	Risk Ratio	Power for N=300	# Events needed in total
40%	52%	1.437	1.300	64.9%	126
40%	55%	1.563	1.375	81.5%	130
40%	57%	1.652	1.425	89.3%	133
40%	59%	1.745	1.475	94.4%	136
40%	61%	1.843	1.525	97.4%	139

Table 7.7: 1 displays the **power achieved for 300** ~~number of~~ **total randomized** patients ~~needed to randomise~~ given a group aggregate ~~conversion~~ **first remission** rate of ~~35~~ **40**% for placebo with two-sided α= 0.10 and a user-defined alpha spending boundary at interim analysis of α=0.01 (two-sided). Group ~~conversion~~ **remission** rates for BI 409306 treatment of

		~~15%, 20%, and 25%~~**52%, 55%, 57%, 59% and 61%** are considered. ~~Sample size considerations for 80% and 90% power are displayed.~~ **Total number of events needed to achieve the power reported is also shown.** Given ~~conversion~~ **remission** rates of ~~35~~ **40**% for patients treated with placebo and ~~20~~**57**% for patients treated with BI 409306, the risk ratio is ~~0.57~~ **1.425** (~~equating to a 43% risk reduction~~**implying that patients treated with BI 409306 will have 42.5% more chance of achieving remission of APS compared to placebo**). ~~and a total sample size of 319 patients is required for 90% power.~~ A sample size of 300 (or 150 per group) was selected as the most logical for establishing proof of concept based on the risk / benefit considerations noted above. **In addition this was the sample size used in the previous protocol and is kept the same.** This translates to ~~88~~**89**% power. **The type I error was selected to be 10% since this is a phase II study meant to provide an understanding of the effectiveness of the drug without being too strict as in a confirmatory setting.** ~~Seventy five~~ **One hundred and thirty three** (~~75~~**133**) events (~~conversions~~ **remissions**) are needed to be observed to meet the trial objectives. This will not be an event driven trial, so the trial will end when all randomised patients have reached 12 months exposure, regardless of number of ~~conversions~~ **remissions** observed. However, a blinded sample size assessment will be performed (see Section 7.4) that may allow for an increase in sample size in an attempt to observe the number of ~~conversions~~ **remissions** necessary for full power.
Rationale for change		To reflect change in primary endpoint.
Section to be changed		9 References
Description of change		The following references were added: **R16-0991** **R18-0654**
Rationale for change		References added in section 1and 7.
Section to be changed		10.2 Ocular Safety Sub-Study
Description of change		Addition of Ocular safety sub-study
Rationale for change		Section added to provide information on the background, patient selection, design, procedures, endpoints, analytical determination and statistical considerations for the ocular safety sub-study.

APPROVAL / SIGNATURE PAGE

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Title: A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	05 Oct 2018 12:44 CEST
Approval-Clinical Trial Leader		05 Oct 2018 12:45 CEST
Approval-Team Member Medicine		05 Oct 2018 20:24 CEST
Approval-Therapeutic Area [redacted]		08 Oct 2018 10:24 CEST
Verification-Paper Signature Completion		08 Oct 2018 12:09 CEST

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Meaning of Signature	Signed by	Date Signed