Clinical Trial Protocol

	Document Number:	**c32481549-05**
EudraCT No. **EU Trial No.**	2020-003760-11	
BI Trial No.	1346-0011	
BI Investigational Medicinal Product(s)	Iclepertin	
Title	A phase III randomized, double-blind, placebo-controlled parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-1)	
Lay Title	Clinical trial of Iclepertin effect on cognition and functional capacity in schizophrenia.	
Clinical Phase	III	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted]	
Version and Date	**Version: 5.0**	**Date: 25 Jun 2024**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	26 Nov 2020
Revision date	25 Jun 2024
BI trial number	1346-0011
Title of trial	A phase III randomized, double-blind, placebo-controlled parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26-week treatment period in patients with schizophrenia (CONNEX-1)
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre in approximately 14 countries
Clinical phase	III
Trial rationale	Cognitive impairment, a core feature of schizophrenia, has been shown to be a major determinant of poor functional outcome. Currently there is no pharmacological treatment available. Inhibition of GLYT1 by Iclepertin may lead to improvement of cognition by improving signalling via N-methyl-D-aspartate (NMDA) receptors. Proof of clinical concept was demonstrated in the phase II, 12 week trial. This registration trial aims to confirm the efficacy, safety and tolerability of Iclepertin in improving cognition and functioning in patients with schizophrenia treated over 6 months (26 weeks).
Trial objective(s)	The primary objective is to assess the efficacy in improving cognitive impairment using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) in patients with schizophrenia treated for 26 weeks with Iclepertin 10mg as compared to placebo. The key secondary objective is to assess the efficacy in daily functioning using Schizophrenia Cognition Rating Scale (SCoRS) and Virtual Reality Functional Capacity Assessment Tool (VRFCAT) in patients with schizophrenia treated for 26-week treatment with Iclepertin 10mg as compared to placebo. The other secondary objectives are to assess the efficacy in improving reasoning and problem solving and patients' experience of cognitive impairment associated with their disease.

	Patients will be required to be on stable antipsychotic treatment at the time of inclusion. The primary treatment effect of interest is defined in the primary estimand framework as specified in detail in Section 7. All efforts will be taken to continue to collect efficacy data at planned visits after patients discontinued trial treatment following an intercurrent event. For patients who discontinued trial treatment after intercurrent events that will be handled by the treatment policy approach, these observed off-treatment data will be included in the primary analysis. For patients who discontinued trial treatment after other intercurrent events that will not be handled by the treatment policy approach, these observed off-treatment data will be censored and excluded from the primary analysis. In summary, the primary treatment effect of interest is the effect obtained at the primary time point if patients had stayed on the treatment, i.e. taking the trial medication for the full treatment duration while allowing the following intercurrent events: change in concomitant medications or background non-pharmacological therapy, change in study partner, and treatment interruption or discontinuation due to exacerbation, an acute episode, adverse events (AEs) that are considered drug related and protocol-defined drug withdrawal.
Trial endpoints	The primary endpoint include: • Change from baseline in overall composite T-score of the MCCB after 26 weeks of treatment. The key secondary efficacy endpoints include: • Change from baseline in the SCoRS interviewer total score after 26 weeks of treatment. • Change from baseline to Week 26 in the adjusted total time T-score in the VRFCAT The secondary efficacy endpoints include: • Change from baseline to week 26 in the T-score of number of correct responses on Tower of London (ToL). • Change in Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) total score from screening visit 1a to Week 24
Trial design	A 26-week, multi-center, multi-national, randomized, double-blind, placebo controlled, parallel group trial.
Total number of patients randomised	586
Number of patients on each treatment	293

Diagnosis	Clinically stable outpatients with established diagnosis of Schizophrenia.
Main in- and exclusion criteria	**Main Inclusion:** • Male or female patients who are 18-50 years (inclusive) of age at time of consent. • Diagnosis of schizophrenia utilizing Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) with the following clinical features: o Outpatient, clinically stable and in the residual (non-acute) phase of their illness. o No hospitalization[1] or increase in level of psychiatric care[2] due to worsening of schizophrenia within 12 weeks prior to randomization. o PANSS score: items P1, P3-P6 ≤ 5 and item P2 and P7 ≤ 4 at Visit 1, and confirmed at Visit 2. • Patients should have functional impairment in day-to-day activities such as difficulties following conversation or expressing themselves, difficulties staying focused, difficulties remembering instructions, what to say or how to get to places, per investigator judgement. • Patients maintained on current antipsychotic treatment (minimum 1 and maximum 2 antipsychotics, but clozapine is not allowed) for at least 12 weeks and on current dose for at least 35 days prior to randomization. • Patients with any other concomitant psychoactive medications (except for anticholinergics) need to be maintained on same drug for at least 12 weeks and on current dose/ regimen for at least 35 days prior to randomization. • Have a study partner, defined as any person who knows the patient well, who has been capable of interacting with the patient on a regular basis, preferably consistent throughout the study, either private or professional. **Main Exclusion:** • Participant with current DSM-5 diagnosis other than Schizophrenia, including but not limited to bipolar, schizoaffective, major depressive disorder etc. M.I.N.I. for psychotic disorders should be used for guidance.

[1] This includes home hospitalization for exacerbation in countries where it applies, however **NOT** hospitalization for social management and/or day programs.
[2] This includes home hospitalization, partial (day-time) hospitalization, or ER visits.

	• Cognitive impairment due to developmental, neurological (e.g., epilepsy, stroke) or other disorders including head trauma, or patients with dementia. • Any suicidal behavior in the past 1-year prior to screening and during the screening period. • Suicidal ideation of type 5 in the C-SSRS in the past 3 months prior to screening and up to and including Visit 2. • Patients with Suicidal Ideation type 4 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan), within 3 months prior to screening and up to and including Visit 2, can be randomized in the study, if assessed and documented by a licensed mental health professional that there is no immediate risk of suicide. • Haemoglobin (Hb) below lower limit of normal at Visit 1 assessed by the central lab.
Test product(s)	Iclepertin
dose	10 mg q.d.
mode of administration	Oral (p.o.)
Comparator product(s)	Matching placebo
dose	Not applicable
mode of administration	Tablet, p.o.
Duration of treatment	26 weeks
Statistical methods	Restricted maximum likelihood (REML) based approach using a mixed effects model with repeated measures (MMRM) will be utilized as the main estimator of the primary estimand on the primary endpoint. Intercurrent events will be handled as specified in Section 7 and missing data as a result from this mixed strategy will be handled via MMRM. This MMRM model will include fixed categorical effects of treatment at each visit, a stratification factor of screening MCCB overall composite T-score (<30, ≥30), and the fixed continuous covariate of baseline MCCB overall composite T-score at each visit. Subject is treated as random effect, and visit will be treated as repeated measure. The primary treatment comparisons will be the contrast between Iclepertin 10mg QD vs. placebo at Week 26. Sensitivity analyses for the primary estimand and analyses based on supplementary estimands are planned to assess the robustness of the results from the primary estimand analysis and the details are provided in Section 7.2.2.

	The testing strategy will follow a gatekeeping procedure defining three families of endpoints/comparisons. Testing for the families of endpoints are illustrated in Section 7.1.

FLOW CHART

Trial Periods and Procedures	**Screening Period** [2]		**Randomized Treatment Period**											**Safety Follow up Period**[11]	
Visit	**1**	**1a**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EOT**[11]/ **11**[12]	**eEoT**[13]	**F1**[11]	**F2**
Weeks	**Screening**		**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**26**	Within 7 days of IMP discontinuation	**EoT/ eEOT +14**	**EoT/ eEoT +28**
Days from first randomized treatment	**-35 to 0**		**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**183**			
Visit time window (days)	-35 to -28	-14 to -7	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3		+3 days	+7 days
Informed consents[1]	X														
Demographics	X														
Medical History	X														
Height	X														
Physical examination	X		X			X			X			X	X		(X)
Weight	X		X			X			X			X	X	(X)	(X)
Vital signs	X		X			X			X			X	X	(X)	(X)
12-lead ECG	X		X			X			X			X	X		(X)
Drug screen test (urine)[3]	X	(X)	X		X		X		X			X	X		
Pregnancy test[4]	X		X		X		X		X		X	X	X		X
Safety Laboratory tests[3]	X		X		X		X		X	X[10]	X	X	X		X
PK Sampling[5]				X	X		X		X			X	X		
Biobanking sample (optional)[6]			X									X	X		
Speech sample (optional)		X				X					X				
M.I.N.I.	X		X[8]												
In-/exclusion criteria	X		X												
Randomization			X												
[redacted]															
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X		
Contact IRT	X		X	X	X	X	X	X	X	X	X	X	X		X
Duplication check	X														
(re)Dispense & administer trial drug at site			**X**[9]	X	X	X	X	X	X	X	X				
IMP Compliance check				X	X	X	X	X	X	X	X	X	X		
Termination of trial drug												X	X		
MCCB	X		X				X					X	X		
VRFCAT	X		X				X					X	X		
PCRS/SCoRS[18]	X		X				X					X	X		
Tower of London (ToL)	X		X									X	X		
CGI-C												X	X		
CGI-S		X	X				X				X	X	X		
PRECIS		X						X			X		X		
SDS (Sheehan)		X									X		X		
PGI-C												X	X		
PGI-S		X	X								X	X	X		
EQ-5D-5L (patient)		X						X			X		X		
EQ-5D-5L (study partners who are caregivers)			X									X	X		

FLOW CHART (con´t)

Trial Periods and Procedures	**Screening Period** [2]		**Randomized Treatment Period**											**Safety Follow up Period**[11]	
Visit	**1**	**1a**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EOT**[11]/ **11**[12]	**eEoT**[13]	**F1**[11]	**F2**
Weeks	**Screening**		**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**26**	Within 7 days of IMP discontinuation	**EoT/ eEOT +14**	**EoT/ eEoT +28**
Days from first randomized treatment	**-35 to 0**		**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**183**			
Visit time window (days)	-35 to -28	-14 to -7	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3		+3 days	+7 days
SPGI-C												X	X		
SPGI-S			X									X	X		
SCQ (study partners who are caregivers)			X									X	X		
Adverse events[15, 16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCRU	X	X	X	X	X	X	X	X	X	X	X	X	X		
Socioeconomic status		X										X	X		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Substance use [19]	X		X				X					X	X		
C-SSRS[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAS/AIMS/BARS		X			X			X			X	X	X		
PANSS[18]	X		X				X					X	X		
Patient Participation Completion in parental trial												X[11]		X[11]	X[14]
Duration in Hr(~)[7]	6.5	2.5	7.5	1.5	1.5	3.0	5.0	1.0	3.0	1.0	2.0	8.0	9.0	1.0	2.0

Footnotes:

(X) optional assessments at discretion of investigator

[1] For each patient, the main trial and study partner consents must be obtained. Optional consents include biobanking and speech analysis.

[2] The screening period may take up to 35 days with 2 visits. At the second screening visit, urine drug screen may be repeated at discretion of investigators (X) if needed.

[3] Safety lab and/ or drug screen test (urine), may be performed more frequently based on investigator discretion or if required locally.

[4] Pregnancy tests are required for women of child-bearing potential only and may be performed more frequently based on investigator discretion or if required locally. If urine (dipstick) pregnancy test is positive, a serum test is required.

[5] PK pre-dose/ trough sample collection within 30 minutes before IMP dosing. Note: No IMP dosing is applicable to EOT or eEOT vist. PK sample should be taken approximately 24 hours post last dose at the EOT. PK sample should be taken as applicable at the eEOT. For further details please refer to Section 5.3 and Appendix 10.1.

[6] One sample for DNA biobanking will be taken, preferably at Visit 2. However, collection at a later visit is permitted as long as the informed consent for biobanking remains valid. Sample for Plasma and Serum banking purposes will be taken at V2 before first IMP intake and again at (e)EOT.

[7] Duration of assessments and visits indicated in this Flow Chart are approximate estimates, actual time may vary as per site and patient requirements.

[8] At visit 2, the MINI does not need to be repeated however the results from visit 1 should be confirmed and documented in the source documents.

[9] **All Baseline assessments must be completed prior to IMP intake at visit 2.**

[10] Haematology panel A and B only.

[11] Patients who finish the 26 weeks of treatment period in this study, can rollover to the extension trial either after completing the EOT visit (preferred option) or within 2 weeks of EOT (i.e. at scheduled FU1 including vitis window).

[12] Visit 11 will be performed only by patients who discontinue early from trial drug but agree to attend further visits according to protocol.

[13] In case patient discontinues earlier than 26 weeks, conduct (e)EOT and follow up with the patient as described in Section 6.2.5

[14] Completion of patient participation who do not consent to extension study and have completed 26 weeks of treatment period.

[15]For adverse events that suggest potential study medication abuse refer to Section 5.2.6.5 and after the patient stops taking the study medication, refer to Section 5.2.6.6. for monitoring of withdrawal adverse events.

[16]For patient not rolling over to extension study, after the individual patient's end of the trial the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.1.

[17] [redacted] training may be repeated as often as deemed necessary.

[18] Study partner **must** complete the SCoRS and PANSS interviews at least at Visit 2 and EOT (please refer to inclusion criterion # 8)

[19] Details on alcohol, nicotine and caffeine use will be collected.

[20] Additional collection of the C-SSRS at an unscheduled visit may be done based on the investigator's discretion.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
APP	Application
AST	Aspartate aminotransferase
AUC	Area under the Curve
BARS	Barnes Akathisia Rating Scale
BI	Boehringer Ingelheim
BP	Blood pressure
BUN	Blood urea nitrogen
CA	Competent authority
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CIAS	Cognitive Impairment Associated with Schizophrenia
CK	Creatine Kinase
C_{max}	Maximum concentration
CNS	Central Nervous System
COVID-19	Corona Virus Disease -19
CRF	Case Report Form
CRO	Contract Research Organisation
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTL	Clinical Trial Leader
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CRT	Cognitive Remediation Therapy
CYP	Cytochrome P450
DDI	Drug Drug interaction

DILI	Drug Induced Liver Injury
dL	deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSM - 5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
(e) EOT	(early) End of Treatment
EPS	Extrapyramidal symptoms
EQ-5D-5L	EuroQol-5Dimensions-5Levels
EQ- 5D-VAS	EuroQol-5Dimensions Visual Analogue Scale
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	Estimated glomerular filtration rate
GLYT 1	Glycine Transporter 1
HAP	Human abuse potential
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HCRU	Health Care Resource Utilization
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IRT	Interactive Response Technology
ISF	Investigator Site File
LAI	Long acting injectable (antipsychotics)
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCCB	MATRICS consensus cognitive battery
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
M.I.N.I	Mini International Neuropsychiatric Interview
MMRM	Mixed effects Model Repeated Measures
NMDA	N-methyl-D-aspartate
NMDA-R	N-methyl-D-aspartate receptor
NOAEL	No-observed adverse-effect level
NTI	Narrow therapeutic index
OPU	Operative unit
PANSS	Positive and Negative Syndrome Scale
PCP	Phencyclidine
PCRS	Placebo control reminder script
PGI - C	Patient Global Impression of Change
PGI- S	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetics
p.o.	per os (oral)
PoCC	Proof of Clinical Concept
PR	Pulse rate
PRECIS	Patient Reported Experience of Cognitive Impairment in Schizophrenia
q.d.	quaque die (once a day)
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
SAE	Serious Adverse Event
SAS	Simpson Angus Scale
SCoRS	Schizophrenia Cognition Rating Scale
SCQ	Schizophrenia Caregiver Questionnaire

SDS	Sheehan Disability Scale
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SPGI-C	Study Partner Global Impression of Change
SPGI-S	Study Partner Global Impression of Severity
TMS	Transcranial Magnetic Stimulation
ToL	Tower of London
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid stimulating hormone
VRFCAT	Virtual Reality Functional Capacity Assessment Tool
WHO	World health organization
WoCBP	Women of child-bearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Schizophrenia is a serious and chronic mental illness leading to poor quality of life and disability. It has a lifetime prevalence of approximately 1%, with almost equal distribution worldwide and slightly higher incidence in men than women. Schizophrenia is a heterogeneous syndrome typically defined by three clusters of symptoms: positive symptoms, negative symptoms and cognitive impairments.

Cognitive impairments are a core feature of schizophrenia and a major determinant of poor functional outcome. Cognitive impairments in schizophrenia are severe [R10-5111], of at least one standard deviation below cognitive performance of community controls [R15-3853; R15-3854], and comparable to moderate to severe traumatic brain injury [R15-3852]. Due to the typical onset of schizophrenia in early adulthood, the lack of a cure and long-term impairments in day-to-day, social and occupational functioning associated with the disease leads to enormous socioeconomic burden [R20-1422, R20-1423].

Schizophrenia is managed with pharmacological and non-pharmacological treatments. Antipsychotics are the primary medication for schizophrenia, with major effects on the reduction of 'psychotic' symptoms and prevention of relapses (maintenance) but demonstrate virtually no beneficial effects on cognition in schizophrenia [R15-5596; R15-5580; R18-1825]. Antipsychotics also adversely affect some aspects of cognitive function, such as processing speed [R15-5595]. Non-pharmacological treatments such as cognitive remediation therapy require specialised expertise and are therefore less widely used [R16-2165; R16-1363].

Data from several cross-sectional and longitudinal studies suggest that ameliorating cognitive deficits can benefit a range of functional measures, which may have significant economic impact [R10-5108]. The potential to increase functional recovery is therefore a major unmet medical need and drives developing novel treatments for Cognitive Impairment Associated with Schizophrenia (CIAS).

It has been long hypothesized that deficits in glutamatergic signaling plays a key role in neuropathology of schizophrenia, particularly negative and cognitive symptoms [R13-4521]. Various glutamatergic transmission-enhancing agents have been tested for the treatment of negative symptoms and/or cognitive impairments in patients with schizophrenia, and produced inconsistent results. Most of these studies were of a small sample size, making interpretation of data difficult [R15-5877; R15-5838; R15-5584; R15-5615; R15-5578; R15-5639; R13-4524; R13-4448; R15-5616].

The majority of large, industry-sponsored studies testing various compounds in CIAS have failed to show proof-of concept. The exception was encenicline (nicotinic alpha 7 agonist), showing improvement of cognition in patients with schizophrenia in Phase II [R16-2465], however these

promising results were not confirmed in Phase III. So far, no drug has been approved for the treatment of CIAS and Iclepertin has the chance to be first medication for CIAS.

1.2 DRUG PROFILE

Iclepertin is a glycine transporter 1 (GLYT1) inhibitor under development for treatment of CIAS. Iclepertin improved cognition in patients with schizophrenia in Phase II, achieving proof-of-clinical-concept.

1.2.1 Mode of action

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

Enhancing glutamatergic neurotransmission is believed to improve brain plasticity (also referred to as neuroplasticity) which is essential for learning and memory. Indeed, pre-clinical studies with Iclepertin have demonstrated pro-cognitive properties in relevant animal models of learning and memory and Phase II results showed beneficial effect on cognition that is known to be impaired in patients with schizophrenia. It is therefore expected that treatment with Iclepertin has the potential to improve cognition that was impaired by the schizophrenia illness.

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of Iclepertin is defined as 12 days after the last dose of trial medication. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

1.2.3 Data from non-clinical and toxicology studies

In vivo target engagement in brain showed a dose-dependent increase of glycine in rat CSF, with a ~50% increase at CSF levels of Iclepertin of ~1x GLYT1 IC50 (U13-2547). Exposure leading to this level of glycine increase is expected to produce clinical efficacy.

Iclepertin has been tested in a comprehensive package of safety pharmacology, genetic toxicology, fertility and early embryonic development, embryo-foetal development, and repeat-dose toxicology studies up to 39 weeks of dosing. Results of these studies support clinical trials in adults for chronic administration, including women of childbearing potential (WoCBP).

Iclepertin has two major human metabolites, [redacted]. These metabolites do not show any relevant activity on GlyT1 and GlyT2, nor against other off-targets tested, nor did they show any pharmacological or toxicological activity.
Iclepertin is primarily metabolized by hepatic CYP3A4 and clinical drug-drug interaction (DDI) studies were conducted (see Section 1.2.4).

Human exposure to Iclepertin up to the no-observed-adverse-effect level (NOAEL) exposure in the most sensitive species (minipig, maximum measured plasma concentration [Cmax] 1430 nM and area under the concentration-time curve [AUC0-24 h] 26500 nM·h) is considered safe. The 10 mg dose to be tested in Phase III is below the no-observed adverse-effect level (NOAEL) with multiple exposures at 10 mg in humans 6-7x below the NOAEL.

1.2.4 Clinical Pharmacology

Iclepertin has a half-life ranging from 37 to 59 h. Steady state is reached after 6 days of dosing with accumulation ratios for C_{max} ranging from 1.96 to 2.63 and for AUC from 2.31 to 3.21. In the single rising dose study 1346.1 (c02820512) at 25 mg dose the effect of a high calorie, high fat meal resulted in an increased exposure with fed/fasted ratio for C_{max} 142% and for $AUC_{0\text{-}tz}$ 126%.The multiple rising dose study 1346.2 (c03572014) looked at the effect of a light meal, and the effect is much less pronounced. In phase II, patients were allowed to take Iclepertin "with or without" food as no clinically relevant effect on exposure was expected. In Phase III 10mg Iclepertin will also be administered with or without food as the expected increase of exposure is below the exposure already observed in previous trials, e.g. 1346-0009 (c31477880).

As the mechanism of action involves enhancement of brain plasticity (which is higher during day than during night), dosing should occur after waking up (i.e. preferably in the morning). Pharmacokinetic parameters between young and elderly healthy subjects, and between Japanese, Chinese and Caucasian subjects are comparable.

Iclepertin crosses blood-brain barrier and the required 50% glycine increase in the CSF was observed after multiple dosing of 10 mg Iclepertin.

Iclepertin is a sensitive substrate of CYP3A4, and co-administration of moderate to strong CYP3A4 inducers / inhibitors is not permitted, as this reduces / increases plasma concentrations of Iclepertin. CYP3A4 sensitive drugs with narrow therapeutic index (NTI) are restricted during the treatment period. For CYP3A4 sensitive drugs without NTI investigators should assess if dose adjustments and/or monitoring of the underlying disease is clinically required for patients who are taking such drugs.List of prohibited medication is inserted in the ISF, although the impact on common comedication in this target population is minimal.Details can be found in Investigator Brochure that is updated and provided to sites at regular intervals.

1.2.5 Data from clinical studies

To date, Iclepertin has been well tolerated and has demonstrated a good safety profile. A total of 323 healthy subjects have received ≥1 dose of Iclepertin. In addition, 339 patients with schizophrenia and 490 patients with Alzheimer's disease have been treated with Iclepertin for 12 weeks. The most frequent AEs were related to the Central Nervous System (CNS), with headaches the most common and more frequent in the active groups than in placebo groups. Dizziness, somnolence and gastrointestinal disorders, such as nausea and vomiting, were also among the AEs reported more frequently on Iclepertin than placebo.

Phase II trials of 12-week treatment duration in patients with schizophrenia and Alzheimer's disease, like trials with other GLYT1 inhibitors such as bitopertin [R15-1266, R18-1054], detected an impact of Iclepertin on haemoglobin (Hb) levels. There was a slight decrease in Hb across the active treatment groups, compared to placebo. It should be however noted that majority of patients (over 90%) remained in the range of normal values.

There were no other clinically relevant findings in the clinical laboratory evaluation, 12-lead electrocardiogram (ECG), assessment of vital signs, or visual tests. No signal was observed for suicidal ideation or behaviour.

In the Phase II trial, 1346-0009, in patients with schizophrenia, proof of clinical concept (PoCC) was demonstrated. Iclepertin improved cognition assessed as the change from baseline in MCCB (Measurement and Treatment Research to Improve Cognition in Schizophrenia [MATRICS] consensus cognitive battery) overall composite T-score after 12-week treatment (the primary endpoint). The largest improvements from baseline versus placebo were observed in the 10 and 25 mg dose groups; the 25 mg dose did not appear to provide an additional benefit over the 10 mg dose. Moreover, the 10 mg group showed most consistent efficacy across various analyses.

In the Phase II trial, 1346.23, in patients with mild to moderate AD, results showed no evidence for efficacy of Iclepertin compared with placebo for the evaluated endpoints.

1.2.6 Summary

In summary, the non-clinical and clinical Iclepertin data demonstrated an acceptable profile to support clinical trials in males and females, including WoCBP, for oral doses of 10 mg once a day, for chronic dosing, in patients with schizophrenia.

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

1.3 RATIONALE FOR PERFORMING THE TRIAL

Cognitive impairment, a core feature of schizophrenia [R14-3766], has been shown to be a major determinant of poor functional outcome, especially in the areas of interpersonal functioning and

educational/vocational performance [R15-0570, R15-0567, R18-1769, R18-1770, R18-1768]. Patients with schizophrenia perform significantly worse than controls on almost all neuropsychological tests [R15-0568]. While many neuropsychiatric disorders are associated with some degree of cognitive dysfunction, the impairments seen in schizophrenia tend to be severe, leading to functional disability for life. Unfortunately there is no pharmacological treatment available.

Iclepertin is a glycine transporter (GLYT1) inhibitor. Inhibition of GLYT1 increases the concentration of the NMDA receptor co-activator glycine in the synaptic cleft thus allowing for improved signalling via NMDA receptors, which may lead to improvement of cognitive symptoms in patients with schizophrenia.

The efficacy and safety of Iclepertin has been investigated in patients with cognitive impairment due to schizophrenia in a trial of up to 12 weeks of treatment duration. In the Phase II trial 1346-0009, a total of 339 patients were exposed to Iclepertin at doses of 2 mg, 5 mg, 10 mg, and 25 mg qd. The PoCC was demonstrated for the primary endpoint of change from baseline in MCCB overall composite T-score after 12-week treatment.

Regulatory guidance requires proven efficacy and acceptable safety of potential pro-cognitive compounds to be demonstrated over at least 6 months. Therefore, the rationale of this registration trial is to confirm the efficacy, safety, and tolerability of Iclepertin in improving cognition and functioning in patients with schizophrenia, when administered for 6 months (26 weeks)in combination with standard-of-care therapy for schizophrenia.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies. As part of this research program, speech sample collection will be done in order to address future scientific questions as described in section 5.6.1.

A separate ocular substudy in selected countries will be conducted. These procedures will be described in detail and implemented via local amendments in the country(ies) planned to participate in this sub-study.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Based on non-clinical data, clinical data from other compounds in the same class, healthy subjects exposed in Phase I trials, and patients treated in Phase II trials, Iclepertin is generally considered to be safe and well tolerated.

In addition, all randomized subjects will be on maintenance treatment with antipsychotic and other psychotropic medications. New concomitant medications may be prescribed as necessary to ensure the welfare of the subject.

Although this is an experimental drug and an individual benefit cannot be guaranteed, PoCC Phase II trial demonstrated efficacy on cognition as assessed using MCCB overall composite T-score in patients with schizophrenia.

So far the acquired clinical data suggest that Iclepertin improves cognition and this improved cognition should lead to functional improvement in day-to-day activities. Patients with functional impairment in day-to-day activities such as difficulties following conversation or expressing themselves, with difficulties to stay focused, difficulties to remember instructions, what to say or how to get to places, could potentially benefit from treatment with Iclepertin.

Patients who complete 26 weeks of treatment in this protocol, will be offered the opportunity to participate in a long term safety extension study with Iclepertin 10 mg.

1.4.2 Risks

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

In the Phase II trial 1346-0009, no dose dependency was observed for the overall number of AEs. The frequency of patients with SAEs was low and was comparable across all treatment groups. The frequency of patients with AEs leading to discontinuation of trial medication was also low. There were no deaths.

Table 1.4.2:1 Overview over trial related risks

Possible/ known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product		
The most frequent AEs were CNS-related • Headache- reversible and can be clinically monitored. • Somnolence (drowsiness)	These effects are understood to be typically mild to moderate and transient. Refer to IB for more details.	Management of symptoms, evaluation, and follow-up as needed to ensure subject safety, per investigators clinical judgment.
Decrease in Hb	• GLYT1 is present on erythrocyte precursors in the bone marrow and on circulating reticulocytes and glycine is required for Hb synthesis. • No clear decrease in Hb was seen in Iclepertin -treated subjects compared to placebo in phase I. • In Phase II, the mean decrease in Hb was observed for 10 mg and 25 mg compared to placebo [10 mg: -3.3 g/L (-0.33 g/dL); 25 mg: -4.5 g/L (-0.45 g/dL); placebo: -0.5 g/L (0.05g/dL)]	• Patients with haemoglobin (Hb) below lower limit of normal at Visit 1 assessed by the central lab will be excluded from participation in this study. • For other GLYT1 inhibitors maximum decrease in Hb was observed after 4 months of treatment, Hb will be checked at Visit 9. • Please refer to section 5.2.6.4 'Haemoglobin and anemia' for more details.

Table 1.4.2:1 Overview over trial related risks (con't)

Possible/ known risks of clinical relevance for this trial	• **Summary of data, rationale for the risk**	• **Mitigation strategy**
Ocular AEs	• The ocular safety of Iclepertin and its effects on ophthalmologic physiology in patient with schizophrenia were characterised in an ocular substudy as part of trial 1346-0009, in which a subset of patients underwent special ocular safety assessments. • No meaningful changes from baseline or differences between Iclepertin treatment groups and placebo were observed with regards to the analysed ocular safety variables.	• Ocular AEs will be monitored and followed up per investigators judgment (refer to Section 5.2.6.3). • Verbatim description for each ocular AE is needed • For ocular AEs the patients must be sent to an ophthalmologist for detailed evaluation. Report from the ophthalmology examination will need to be collected.
Iclepertin - Drug Interactions		
Moderate or strong CYP3A4 inhibitors	Exposure of Iclepertin will increase in the presence of the moderate or strong CYP3A4 inhibitors	Patients should not be randomized if taking any of the drugs listed in the ISF or need such drug during treatment period (refer section 4.2.2.1). Patients requiring Paxlovid (a strong CYP3A inhibitor) for the treatment of COVID-19 during the trial should stop taking Iclepertin at time point of Paxlovid start, and restart Iclepertin 1 day after Paxlovid cessation.
CYP3A4 sensitive drugs with narrow therapeutic index (NTI)	Exposure of CYP3A4 sensitive drugs with NTI decreases during treatment with Iclepertin	

Table 1.4.2:1 Overview over trial related risks (con't)

Possible/ known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Disease Related Risk		
Worsening of Schizophrenia or relapse	Clinically stable patients with schizophrenia are randomized to this study. Schizophrenia is a cycling disease with fluctuation of symptom severity: acute episodes (e.g., relapse) and intervals of relative stability (e.g., remission) between them.	Monitoring of symptoms of schizophrenia with adjustment of maintenance Standard of Care (SoC) treatment to control symptoms. Definition of relapse provided to monitor in a standardized manner.
Potential worsening of existing or new side effects caused by **treatment with antipsychotics** (e.g. tardive dyskinesia, metabolic, orthostatic hypotension)	No worsening of the AEs due to antipsychotic treatment were seen in the phase II study.	AE monitoring Extrapyramidal symptoms (EPS) assessed using Simpson Angus Scale (SAS)/ Abnormal Involuntary Movement Scale (AIMS)/ Barnes Akathisia Rating Scale (BARS) throughout treatment period Per investigator judgement adjustment of background medication is allowed.
Suicidality	Suicidal behavior and suicidal ideation are common in this population. However, patients are in psychiatric treatment where continuous assessment of suicidal behavior and risk is part of the standard of care. Frequency of suicidal ideation/behavior reported for Iclepertin groups was numerically similar to that reported for the placebo group in Phase II trial in patients with schizophrenia.	Prospective assessment of suicidal ideation and behavior is included in this study using the Columbia Suicide Severity Rating Scale (C-SSRS). In case of a positive report of suicidal behavior and/or suicidal ideation additional collection of the C-SSRS at any frequency and/or any medical interventions and sufficient follow-up may be done based on the investigator's discretion.

Table 1.4.2:1 Overview over trial related risks (con't)

Possible/ known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Other risks		
Potential risk while operating machinery	General precaution for CNS active drugs	It is recommended that subjects should exercise caution when driving or operating machinery after drug administration.
Human abuse potential	According to the 2017 FDA guidance on "Assessment of Abuse Potential of Drugs", assessment of human abuse potential (HAP) is required for drug products "that contain CNS-active new molecular entities (NMEs)". Based on nonclinical data, completed Phase I studies and assessment of data from one completed Phase II trial in CIAS with Iclepertin, no signal of human abuse potential has been observed however human abuse liability of Iclepertin has not been formally investigated.	A list of AEs for assessment of potential abuse liability of Iclepertin, will be provided as part of ISF and relevant AEs must be reported including a verbatim description. Investigators will be trained about the importance to assess patients for abuse and withdrawal related adverse events. Detailed information will be collected and monitored for study medication compliance >100%
Drug-induced liver injury (DILI)	DILI is a rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.

Table 1.4.2:1 Overview over trial related risks (con't)

Possible/ known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	• **Mitigation strategy**
• **Other risks**		
Genotoxicity, fertility and teratogenicity	Iclepertin and its metabolites ([redacted] and [redacted]): • Showed no evidence of genotoxicity. • Demonstrated no effects on fertility and no evidence of teratogenicity.	• Based on this evaluation, contraception for male clinical trial participants (or their sexual partners) is not required. • WoCBP will need to use highly effective method of contraceptives with failure rate <1%

Table 1.4.2:1 Overview over trial related risks (con't)

Possible/ known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**• Mitigation strategy**
• Other risks		
Corona Virus Disease -19 (COVID- 19) pandemic	Overall, the risk for patients with schizophrenia participating in the Iclepertin CIAS clinical trials is considered increased in light of COVID-19 pandemic, due to the need for the study participant to leave his/her home, higher prevalence of medical comorbidities such as diabetes, COPD, and cardiovascular disease that may increase the risk of developing COVID-19 related complications. Moreover, decreased Hb due to treatment with Iclepertin may lead to anemia and thus increase the risk of COVID-19 related complications.	In all clinical trials, appropriate risk minimization measures will be taken in accordance with the public health precautions implemented in the country where the study will be conducted (e.g. minimizing time at the clinic, replacement of physical visits with remote visits, minimizing the use of public transportation to the site etc.). Considering the risk, patients with an active SARS-CoV-2 infection within 35 days prior to randomization will be excluded from participation in this study. Also, the study drug should be discontinued from treatment if the patient experiences severe or serious symptomatic infection with SARS-CoV-2. The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the patient.

Table 1.4.2:1 Overview over trial related risks (con't)

Possible/ known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	• **Mitigation strategy**
Placebo risks and risk of stopping the treatment		
Placebo Risks	• There is currently no approved medication indicated for treatment of CIAS. Since an approved, effective comparator is not available for this study, a placebo control group is being used in this study design. • According to the medication assignment planned in this trial, patients will be assigned to placebo or Iclepertin arm 10 mg in 1:1 ratio.	• Inclusion criteria require that patients enrolled in this clinical trial should be clinically stable and on stable SoC treatment with antipsychotic and other psychotropic medications. • Maintenance antipsychotic treatment is needed to prevent relapse of acute psychotic episode. Thus, assignment to the placebo arm or stopping the study drug during the treatment period is not associated with a higher risk of psychotic relapse. • Psychiatric events, positive and negative symptoms, and suicidality will be monitored throughout the study to ensure that worsening of pre-existing conditions or any newly occurring events are detected and any necessary actions taken according to stopping criteria.
Risks of stopping study drug	In the Phase II study, following end-of-treatment, no increases in adverse events were observed in patients treated with Iclepertin in comparison to those treated with placebo. Potential adverse events after stopping study drug have not been formally investigated thus far and therefore cannot be fully excluded.	• Monitoring AEs of interest for assessment of potential abuse liability are described above (refer to placebo risks). • In one of the Phase III studies (c33087946), after completion of 26 weeks of treatment, all patients will be closely monitored during the 4 weeks in the safety follow up period to assess potential adverse events of withdrawal from Iclepertin treatment.

Table 1.4.2:1 Overview over trial related risks (con't)

Possible/ known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	• **Mitigation strategy**
Trial procedures		
General discomfort Blood Draw	The risks of a blood draw include fainting and pain, bruising, swelling, or rarely infection where the needle is inserted. In rare cases a nerve may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch and persistent pain.	• Management of discomfort, evaluation, and follow-up as needed to ensure patient safety.

Given the patient population and the long treatment period there is a risk of premature treatment discontinuation/patient withdrawal. The study has been designed with frequent contacts between trial site and patients ensure the motivation and engagement. This will ensure frequent checks and reinforce compliance to trial treatment and background medication. For further follow-up after premature treatment discontinuation please refer to section 6.2.5.

A Data Monitoring Committee (DMC), independent from the Sponsor, will be established to review the safety data at intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial based on safety assessment. The tasks and responsibilities of the DMC members will be detailed in the DMC charter.

1.4.3 Discussion

Cognitive impairment associated with schizophrenia (CIAS) remains a tremendous scourge on the lives of millions of people across the world. It is the aspect of the illness that most accounts for the social isolation and functional disability that plagues most people with schizophrenia for their entire lives [R20-0592]. Yet, currently approved antipsychotics do not demonstrate relevant efficacy in the treatment of cognitive deficits of schizophrenia.

Given the acceptable safety profile of Iclepertin in clinical, nonclinical and toxicology studies performed to date, the sponsor feels the risks to the participating patients are mitigated by the careful monitoring that is planned during the study. Although individual benefit may not be observed for each patient, this registration trial aims to seek approval of the first pharmacologic

treatment that improves cognition in patients with schizophrenia, which remains a high unmet medical need.

Considering the chronic and severe disease burden of CIAS, main cause of disability in this population, the potential therapeutic benefits are assessed to outweigh the currently understood potential risks of the treatment.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this phase III pivotal trial in CIAS is to assess the efficacy in improving cognitive impairment using MCCB in patients with schizophrenia treated for 26 weeks with Iclepertin 10mg as compared with placebo.

The key secondary objective is to assess the efficacy in daily functioning of 26-week treatment with Iclepertin 10mg as compared with placebo in terms of Schizophrenia Cognition Rating Scale (SCoRS) and Virtual Reality Functional Capacity Assessment Tool (VRFCAT).

The secondary objectives are to assess the efficacy in improving reasoning and problem solving and patients' experience of cognitive impairment associated with their disease.

Patients will be required to be on stable antipsychotic treatment at the time of inclusion.

The primary treatment effect of interest is defined in the primary estimand framework as specified in detail in Section 7. All efforts will be taken to continue to collect efficacy data at planned visits after patients discontinued trial treatment following an intercurrent event. For patients who discontinued trial treatment after intercurrent events that will be handled by the treatment policy approach, these observed off-treatment data will be included in the primary analysis. For patients who discontinued trial treatment after other intercurrent events that will not be handled by the treatment policy approach, these observed off-treatment data will be censored and excluded from the primary analysis.

In summary, the primary treatment effect of interest is the effect obtained at the primary time point if patients had stayed on the treatment, i.e. taking the trial medication for the full treatment duration while allowing the following intercurrent events: change in concomitant medications or background non-pharmacological therapy, change in study partner, and treatment interruption or discontinuation due to exacerbation, an acute episode, adverse events (AEs) that are considered drug related and protocol-defined drug withdrawal.

2.1.2 Primary endpoint(s)

The primary efficacy endpoint is assessing cognition:

- Change from baseline in overall composite T-score of the MCCB after 26 weeks of treatment.

2.1.3 Secondary endpoint(s)

The key secondary efficacy endpoints are:

- Change from baseline in the SCoRS interviewer total score after 26 weeks of treatment
- Change from baseline to Week 26 in the adjusted total time T-score in the VRFCAT

The secondary efficacy endpoints are as follows:

- Change from baseline to Week 26 in the T-score of the number of correct responses on Tower of London.
- Change from screening visit 1a to Week24 in Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) total score

[redacted]

[redacted]

2.2.2.2 Further safety endpoints

- Disease under study monitored using:
- PANSS total score and change from baseline
- Incidence of relapse
- SAS/BARS/AIMS Scale scores throughout the treatment
- Suicidality as assessed by C-SSRS
- Occurrence of protocol specified AESI
- Percentage of patients with (S)AEs (including clinically relevant abnormalities of physical examination, vital signs, ECG test and laboratory tests)

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The overall trial design is as follows (see Figure 3.1:1):

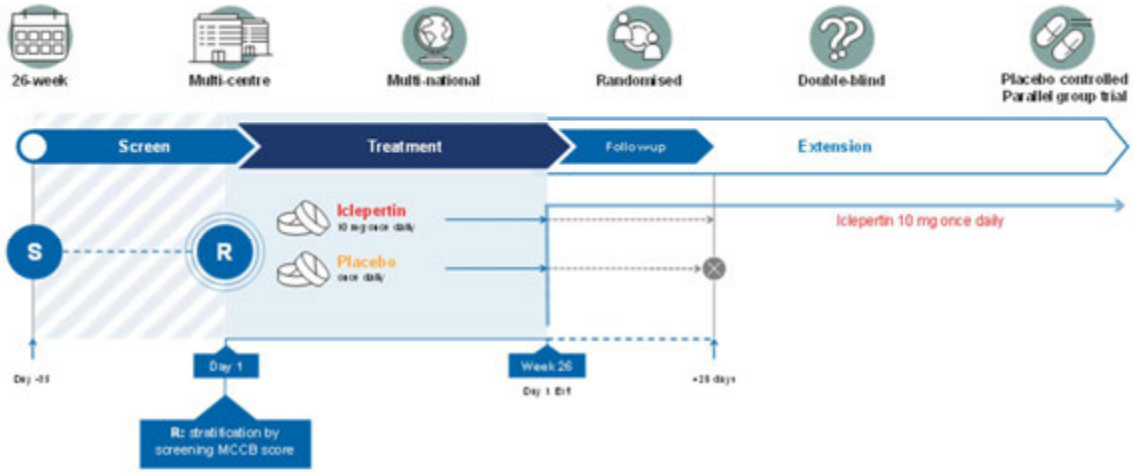

Figure 3.1:1 Trial design

This is a 26-week, multi-center, multi-national, randomized, double-blind, placebo controlled, parallel group trial in patients with schizophrenia. In total, approximately 586 patients with schizophrenia on stable antipsychotic treatment who meet the eligibility criteria are planned to be randomized in equal ratio into this trial.

Patients are enrolled in the trial once informed consent has been signed.
Patients who are deemed eligible by the investigator, after screening, will be randomized to the 26-week treatment period assigned with equal ratio to one of the following arms:

- Iclepertin 10 mg once daily
- Placebo once daily

Randomization of patients will be stratified by MCCB overall composite T-score at screening (screening MCCB overall composite T-score < 30, ≥ 30) and participation in the ocular substudy (Yes, No) via Interactive Response Technology (IRT) to balance the baseline cognitive level among groups.

All patients who finish 26 weeks of treatment with Iclepertin or placebo in this study, will be offered the opportunity for treatment with Iclepertin 10 mg in a long-term safety extension trial. Eligible patients may enter the extension trial preferably after completing the EOT visit, or alternatively within 14 days from EoT (i.e. at FU1 visit including the respective time window).

Subjects who do not enroll in the extension study will be followed up for safety for an additional period of 4 weeks after last dose of medication. For further details please refer to Section 6.2. As part of this research program, optional biobanking and speech sample collection will be done in order to address future scientific questions as described in Section 5.5 and 5.6.1.

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

A parallel group design is appropriate to detect the effects of Iclepertin 10 mg compared to placebo on cognitive impairment in clinically stable patients with schizophrenia. The primary analysis of efficacy is planned after 26 weeks of treatment. Elimination of Iclepertin takes approximately 12 days, therefore 28 days is considered sufficient to detect any unexpected late onset adverse events, to evaluate the pharmacodynamic effect of Iclepertin after discontinuation and to allow for assessment of reversibility of any unexpected side-effects. Refer to Section 5.2.6.4 for follow up of Hb related issues.

Details of the statistical approach and sample size justification are given in Section 7.

There is currently no approved medication indicated for treatment of CIAS and therefore, a placebo control group is being used in this study. It should be noted that all patients, including those randomized to the placebo group, are permitted to remain on other antipsychotic and psychotropic medications, within the eligibility criteria. The risk to the control group is discussed in Section 1.4.

A Data Monitoring Committee (DMC), independent from the Sponsor, will be established to review the safety data at regular intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial based on periodic safety monitoring. The tasks and responsibilities of the DMC members will be detailed in the DMC charter.

3.3 SELECTION OF TRIAL POPULATION

It is planned that approximately 100 trial centres in multiple countries will be participating in this trial and a sufficient number of patients will be screened for the trial to ensure that approximately 586 patients are randomized to trial treatment.

This is a global trial and patients from all ethnic and racial backgrounds may be included.

It is expected that approximately five patients will be randomized at each trial center. If enrolment is delayed, additional sites may be recruited. Sites that do not screen patients over a prolonged period of time may be closed.

Permission to randomize more than 30 patients per site must be obtained from the Clinical Trial Leader (CTL). This will only be allowed after a careful review of the enrolment status of the site.

Screening of patients for this trial is competitive. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

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

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

In this study, it was decided that adult patients up to 50 years of age at the time of consent could participate, as neuroplasticity (i.e. ability of the brain to change during life by acquiring, storing and re-using information) declines with age as well as with duration of the illness and treatment with antipsychotics.

So far, the acquired clinical data suggest that Iclepertin improves cognition which should translate to functional improvement in day-to-day activities. Therefore patients with functional impairments as described in inclusion criterion #4 will be included in this trial.

This trial is investigating Iclepertin as a treatment for cognitive impairment due to schizophrenia and therefore it is hypothesized that Iclepertin will improve cognitive impairment caused by the disease. Patients who are randomized into the trial must have achieved at least an 8th grade education as a surrogate of pre-morbid cognitive capacity.

Retesting

Retesting applies in situations when the issue can be resolved within the screening period of 35 days, for example patients are testing positive on urine drug screen for cannabis or opioids at Visit 1. These patients can be re-tested once (consider long half-life of cannabis) within the screening period of 35 days, if there is a reasonable explanation and expectation that the patient is not a regular user and will not test positive again on re-test, and at the discretion of the investigator.

In case of retesting, the patient will keep the same subject number. The results of all retests should be available within the 35 days of screening period. Once retests are available and negative for the retested parameter, and in case all other eligibility criteria are met, the patient can be randomized on the planned Visit 2 date.

Rescreening of patients

Rescreening of a patient can be done once, if there is a reasonable explanation and expectation that the patient may have become eligible.
Potential reasons for rescreening could be:

- Haemoglobin is too low: Patients with low Hb at screening can be re-screened once the cause of low Hb was successfully treated. The reason and its treatment must be documented in the source documents.
- Active infection with SARS-CoV-2
- Suicidality once the required exclusion period is over
- Clinically significant findings per Investigators judgement
- Stability of Schizophrenia symptoms or medications
- Liver enzyme elevation, e.g., ALT/ AST derangements
- Positive urine drug test at screening visit, if longer wash-out period needed
- Anticholinergic dose exceeding allowed limits, etc.

Background medications should not be adjusted or changed for the purposes of study enrolment or to fulfil eligibility. Changes in background medications should occur per standard of care. Anti-psychotic background therapy must be stable prior to re-screening.

For other potential reasons, please contact the clinical trial leader (CTL).

In case of re-screening, the patient will receive a new subject number. The patient and the study partner must sign the current, approved version of the informed consent before any study specific procedures are performed.

- If rescreening is done within 12 weeks of screening, all procedures **except** MCCB, SCoRS, VRFCAT and Tower of London must be repeated.
- If the rescreening is done more than 12 weeks after the screening, all procedures as shown in the Flow Chart for Visit 1 must be repeated.

For all re-screened patients, the screening period will be again 35 days as per protocol. In case all eligibility criteria are met during these repeated screening procedures, the patient can be randomized on the newly planned Visit 2 date.

3.3.1 Main diagnosis for trial entry

Clinically stable outpatients with established Schizophrenia (as per Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5))

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

3.3.2 Inclusion criteria

1. Patients must be capable of providing signed and dated written informed consent by date of Visit 1 in accordance with ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP) and the local legislation prior to the admission to the trial.

2. Male or female patients who are 18-50 years (inclusive) of age at time of consent.

3. Diagnosis of schizophrenia utilizing DSM-5 with the following clinical features:

    - Outpatient, clinically stable and in the residual (non-acute) phase of their illness.
    - No hospitalization[3] or increase in level of psychiatric care[4] due to worsening of schizophrenia within 12 weeks prior to randomization.
    - PANSS score: items P1, P3-P6 ≤ 5 and item P2 and P7 ≤ 4 at Visit 1, and confirmed at Visit 2.

4. Patients should have functional impairment in day-to-day activities such as difficulties following conversation or expressing themselves, difficulties to stay focused, difficulties to remember instructions, what to say or how to get to places, per investigator judgement.

5. Patients maintained on current antipsychotic treatment (minimum 1 and maximum 2 antipsychotics, but clozapine is not allowed) for at least 12 weeks and on current dose for at least 35 days prior to randomization.
    - For patients on two antipsychotics, at least one antipsychotic must be within the approved label dose range. The second antipsychotic must not exceed the maximum daily dose per local label.

    Note: If the total dose is stable, different dosage forms of the same antipsychotic treatment will be considered as one antipsychotic.

6. Patients with any other concomitant psychoactive medications (except for anticholinergics) need to be maintained on same drug for at least 12 weeks and on current dose/ regimen for at least 35 days prior to randomization.
    - Maximum daily benzodiazepine load of up to 1 mg lorazepam-equivalent. Table of relevant medications and their equivalencies will be provided as a part of ISF.
    - For any other psychoactive medications, doses cannot exceed the maximum daily dose per local label.

[3] This includes home hospitalization for exacerbation in countries where it applies, however NOT hospitalization for social management and/or day programs.
[4] This includes home hospitalization, partial hospitalization or ER visits

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

8. Have a study partner, defined as any person either private or professional who knows the patient well, has been capable of interacting with the patient on regular basis, and preferably consistent throughout the study.
    - The study partner must interact with the subject a minimum 1 hour per week and, preferably, at least 2 times a week. At least one interaction per week should be in person.
    - The study partner must have educational achievement of minimum 8th grade.
    - Professional study partners (e.g. study nurse, social worker etc.) are allowed if not involved in administration of any of the protocol assessments.

9. Patients must, in the investigator's opinion, exhibit reliability and physiologic capability (e.g. sufficient hearing, vision etc.), to comply with all protocol procedures, and have attained an educational achievement of minimum 8th grade.

10. Patients and his/ her study partner must be fluent in the language of the batteries/ questionnaires.

[5] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

3.3.3 Exclusion criteria

1. Participant with current DSM-5 diagnosis other than Schizophrenia, including but not limited to bipolar, schizoaffective, major depressive disorder etc. M.I.N.I. for Psychotic disorders should be used for guidance.

2. Cognitive impairment due to developmental, neurological (e.g., stroke) or other disorders including head trauma, patients with dementia or epilepsy.

3. Severe movement disorders
   - Leading to cognitive impairment (e.g. Parkinson dementia), or
   - Interfering with the efficacy assessments, or
   - Due to antipsychotic treatment that cannot be controlled with low dose anticholinergic treatment (equal to maximum 1 mg benztropine twice daily). Table of relevant medications and their equivalencies will be provided as a part of ISF

4. Any suicidal behavior in the past 1-year prior to screening and during the screening period.

5. Suicidal ideation of type 5 in the C-SSRS (i.e. active suicidal thought with plan and intent) in the past 3 months prior to screening and up to and including Visit 2.
   - Patients with Suicidal Ideation type 4 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan), within 3 months prior to screening and up to and including Visit 2, can be randomized in the study, if assessed and documented by a licensed mental health professional that there is no immediate risk of suicide.

6. History of moderate or severe substance use disorder (other than caffeine and nicotine), as defined in DSM-5 within the last 12 months prior to informed consent.

7. Positive urine drug screen at Visit 1 based on central lab test. For a list of drugs assessed in the urine drug screen, please refer to Table 5.2.3:1.

8. Patients who were treated with any of the following within 6 months prior to randomization:
   - Clozapine
   - Stimulants (e.g. methylphenidate, dextroamphetamine, modafinil)
   - Ketamine or esketamine
   - Electroconvulsive therapy (ECT) or Modified ECT

9. Participation in any investigational psychoactive drug trial (both industry/ academic) in last 6 months, and 30 days or 5 half-lives for no-psychoactive drug trial, prior to randomization.

10. Patients who were previously treated with Iclepertin.

11. Patients who are treated with any of the following within the last 35 days prior to randomization: [6]
    - Strong or moderate CYP3A4 inhibitors including grapefruit juice
    - Strong or moderate CYP3A4 inducers including St. John's wort (Hypericum perforatum)
    - Dietary supplements and herbal remedies that may impact cognition, in the investigator´s judgement
    - Antiepileptics (when used for the treatment of epilepsy)[7]
    - Tricyclic antidepressants
    - Traditional Chinese medicine/ non-Western therapy
    - Medical devices therapy (e.g. TMS, neurofeedback)

12. Patients who plan to change their current life-style habits including but not limited to alcohol, nicotine or caffeine use, or diet, during the treatment period.

13. Patients who have participated in a clinical trial with repeated assessments (i.e. a single assessment is not exclusionary) with the MCCB and/ or any other schizophrenia cognitive battery within 12 weeks prior to screening.

14. Any formal Cognitive Remediation Therapy (CRT) within 12 weeks prior to screening. Initiation of CRT is not allowed during the study.

15. Initiation or change in any type or frequency of psychotherapy (e.g. cognitive behavioral therapy, social skills training, vocational/occupational therapy) within 12 weeks prior to randomization. Patients with ongoing, stable psychotherapy for more than 12 weeks prior to randomization (and intend to maintain the same frequency during the study) may qualify as per clinical judgement of the investigator.

16. Any of the following, in the judgment of the investigator:
    - Clinically significant finding of the physical examination, vital signs (including blood pressure (BP) and pulse rate (PR)), ECG or laboratory value (as measured by the central laboratory) that would jeopardize the patient´s safety while participating in the trial or their capability to participate in the trial.
    - Symptomatic/unstable/uncontrolled or clinically relevant concomitant disease or any other clinical condition that would jeopardize the patient´s safety while participating in the trial or capability to participate in the trial.
    - Significant or unstable physical condition that may require change in medication or hospitalization that would impact cognitive function.

[6] List of relevant medication will be provided as a part of ISF.
[7] Antiepileptics as monotherapy when used for other indications are acceptable if they fulfil criteria detailed in inclusion criteria #6, and should not be started during the treatment period if at all possible.

- Planned major surgery requiring withdrawal from study medication for more than 2 weeks during the study period.

Note: Please contact sponsor in case of you have any questions.

17. Haemoglobin (Hb) below lower limit of normal at Visit 1 assessed by the central lab.

18. History of haemolytic anemia including haemoglobinopathies (for example thalassemia or sickle-cell anemia), RBC membrane diseases orknown G6PDH (Glucose-6-phosphate dehydrogenase) deficiency;current anemia or patients planning to donate blood.

19. Severe renal impairment defined as an eGFR < 30mL/min/1.73m² assessed by the central lab at Visit 1.

20. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 times upper limit of normal assessed by the central lab at visit 1.

21. Known history of HIV and/ or known on-going Hepatitis B or C infections.

22. Patients with known active infection with SARS-CoV-2 within the last 35 days prior to randomization.[8]

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

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

25. Patient who did not complete the MCCB at Visit 1 and therefore does not have T-score for randomization.

26. Patients with an allergy to Iclepertin and/or any of the excipients (including lactose). A list of Iclepertin and placebo ingredients are provided in the Investigators' Brochure.

3.3.4 Withdrawal of patients from treatment or assessments

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the options for follow-up of patients in case of withdrawal.

[8] Testing for SARS-CoV-2 is not the part of this trial. If required this needs to be done per local requirements

Every effort should be made to keep randomized patients in the trial, if possible, or at least to collect important trial data.

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent"). The decision to discontinue trial treatment or withdraw consent for further trial participation along with the reason must be documented in the patient files and electronic Case Report Form (eCRF). If applicable, consider the requirements for Adverse Event collection reporting (Sections 5.2.6.2.1 and 5.2.6.2).

Every effort should be made to keep randomized patients on background medication with antipsychotics to prevent relapse.

Every effort should be made to prevent patients from being lost to follow-up. If a patient does not come in for a planned visit, please refer to the retention guide for guidance regarding frequency and methods to reach out to patient and/or study partner.

3.3.4.1 Temporary Trial Treatment Discontinuation

Temporary trial treatment discontinuation is permitted. For treatment interruptions of > 10 days, the sponsor should be informed.

Reasons of temporary trial treatment discontinuation and exact start and end dates must be documented in source documents.

Reasons for temporary drug discontinuation could be due to:

- Severe or serious symptomatic infection with SARS-CoV-2.
- Current treatment with Paxlovid.
- Other medical condition(s), per investigator judgment.

Patients who prematurely discontinue trial medication are allowed to restart treatment, if appropriate, in the opinion of the Investigator.

3.3.4.2 Permanent Discontinuation of Trial Treatment

For all patients the reason for permanent discontinuation from trial treatment (e.g. adverse events) must be recorded in the eCRF. Patients who permanently discontinue from the trial after randomization will not be replaced.

Even if the trial treatment is permanently discontinued, the patient should remain in the trial and, given the patient's agreement:

- The patient will complete the early end of treatment and safety follow up visits.
- Additionally, the patient will be followed according to the Flow Chart until the planned Visit 11 (26 weeks).

Please refer to Flow Chart and Section 6.2.5 for more information on continued trial participation.

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

- The patient wants to stop taking the trial treatment permanently.
- 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) that per certified trained mental health professional constitutes a risk of suicidal behaviour
- The Hb drops below 100 g/L (10g/dL) OR

  Hb decreases by 25% or more from baseline and is below the lower limit of normal.
- The patient can no longer be treated with trial medication for serious medical reasons (e.g., liver injury, stroke, etc.), per investigator's clinical judgement.
- The patient needs to take any restricted medication that may impact the patient's safety to continue the treatment, per investigator´s clinical judgement. Please consult with sponsor.
- Pregnancy: if a patient becomes pregnant during the trial the study medication will be stopped, the patient will be discontinued from the trial and the patient will be followed up until birth or otherwise termination of the pregnancy.
  - For further information, including the process for follow-up on the outcome of the pregnancy please see Section 5.2.6.7.

If new efficacy/ safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

3.3.4.3 Withdrawal of consent to trial participation

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

Withdrawal of consent to trial participation means permanently stopping the study treatment, plus no further participation in study visits, study assessments plus no further contact with the

patient and/or data collection (e.g. through patients representative, medical records, as permitted by local regulations).

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between "trial treatment discontinuation" and "withdrawal of consent to trial participation", as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 6.2.5.

3.3.4.4 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. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in Section 3.3.4.2
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

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

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

- Iclepertin 10 mg once daily for 26 weeks
- Placebo once daily for 26 weeks

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product

Substance:	Iclepertin
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	10 mg
Posology:	1 tablet once daily
Method and route of administration:	Oral

The characteristics of the reference product are as shown below.

Table 4.1.1: 2 Reference product

Substance:	Placebo matching Iclepertin 10 mg
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable
Posology	1 tablet once daily
Method and route of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

The dose was selected based on the following strategy:

1. The effective dose in improving cognition in the PoCC/dose finding trial in patients with schizophrenia was 10 mg, as this dose separated best from placebo with regards to the primary efficacy endpoint in the phase II trial.
2. Iclepertin was well tolerated in patients with schizophrenia up to 25 mg once daily for 12 weeks.
3. Decrease in Hb was dose dependent but a small decrease of 3.3 g/L in 10mg group and 4.5 g/L in 25mg was observed. Hb will be monitored.
4. Iclepertin was well tolerated in healthy subjects in single doses of up to 150 mg and multiple doses of up to 75 mg bid (150 mg per day).
5. Iclepertin showed efficacy at doses which correspond to ~50% glycine increase in CSF and CSF levels of the drug in the range of 1x GLYT1 IC50. The dose of 10mg fulfils this criteria.
6. In the Proof of Mechanism trial (c03724403) the target mean increase of 50% in CSF glycine was observed after multiple dosing of 10 mg Iclepertin in healthy volunteers.

Consequently, the dose of 10 mg once daily of Iclepertin will be tested in Phase III pivotal studies.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 1:1 ratio at visit 2 via Interactive Response Technology (IRT). Note that the medication kit numbers are different from the patient number (the latter is generated during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

Dispensing of medication kits for the double-blind treatment period will begin at Visit 2. Throughout the treatment period, 2 trial medication kits will be provided at each visit. Medication assignment will be provided through IRT. The assigned medication kit numbers must be entered in the eCRF, and the corresponding medication kits must be given to the patient. The duration of treatment is 26 weeks. At each of the visits, patients will receive supplies for a total of 4 weeks (21 treatment days plus 7 days reserve).

The first dose of study medication will be taken at the end of Visit 2 under supervision of the investigator or delegated site staff, after all Visit 2 assessments have been completed. In case the Visit 2 is split into 2 sequential days, the first dose of study medication should be taken on the second day of split the visit, after all Visit 2 assessments have been completed.

Throughout the study, patients should be instructed to take 1 tablet orally with water and with or without food after waking up. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled.

Patients should be instructed **not** to take their trial medication AT HOME on each visit day as patients will be dosed at the site. Dosing should occur approximately 24 hours after the drug administration of the preceeding day.

The last dose of study medication should be taken on the day before the EoT Visit. In case the EoT Visit is split into 2 sequential days, the last dose of study medication should be taken on the day before the first day of the split visit.

On longer visit days the dosing may occur in the afternoon.

A dose reduction of Iclepertin is not possible.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Except for independent DMC, patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regards to the randomised treatment assignments until the database is declared ready for analysis according to the sponsor's SOPs. Further details regarding the timepoint of unblinding the database for anlaysis are documented in the TSAP.
The access to the randomisation code will be kept restricted until its release for analysis.

Long-term treatment with GLYT1 inhibitors such as Iclepertin may reduce Hb levels in some patients. Phase II results from the 1346-0009 trial showed that the majority of patients (over 90%) have Hb levels that remain in the normal range (c31477880 table 15.3.2.2.). It is also noted that decreases in Hb have also been observed in some placebo patients, as there can be considerable fluctuation in Hb values. The number of patients with decreased Hb, by at least >2 g/dl, was the same in placebo group, as in the active treatment arms (c31477880). Therefore, reductions in Hb may not permit investigators to infer which treatment arm individual patients had been allocated to.

Nonetheless, in order to ensure the double-blind nature of the trial, the Hb related parameters will be blinded to the investigator and sponsor starting at visit 2 until the end of trial. The site will receive alerts as detailed in Section 5.2.6.4. The Hb related parameters will be reviewed throughout the trial by an independent, third party as well as by the independent DMC. For medical management of any patient with an alert on decreased Hb, refer to Section 5.2.6.4.

The responsible bioanalyst of the external bioanalytical laboratory will receive the randomization codes prior to last patient completed to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients.

The trial bioanalyst (TBA) may receive unblinding data from external bioanalytical laboratory after the last patient completed the last visit but prior to official unblinding of the trial database for preparation of data transfer (e.g. check file structure prior to data upload and SDTM transformation and bioanalytical report writing).

Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblended.

4.1.5.2 Unblinding and breaking the code

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

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

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal 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.
For details of packaging and the description of the label, refer to the ISF.

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

4.1.7 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee,

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

Investigational drugs are not allowed to be used outside the context of this protocol. Patients must be instructed to not share or permit others to use their study medication. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug. In the event that the patient does not return all medication, the investigator or designee is required to obtain an explanation from the patient as to why not all medication was returned (e.g. if the blister card was discarded by accident, lost medication or medication taken by another person, etc.).
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the appointed CRO, the investigator or designee 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

Throughout the duration of the trial patients should continue to take their current antipsychotic and concomitant psychotropic medications, the dose of which should remain unchanged if at all possible. These medications will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

Any change in dose of antipsychotic and concomitant psychotropic medications should be recorded in the source documentation and on the appropriate pages of the eCRF. Any additional treatment that is considered necessary for the patient's welfare may be given at the discretion of the investigator.

Only patients with stable schizophrenia are included in this trial. As such, no rescue medication or emergency procedures are foreseen for this trial. In case of worsening of schizophrenia, any treatment adjustment deemed necessary per clinical judgment can be given.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medications and non-pharmacological interventions that are exclusionary under the **eligibility criteria** (Section 3.3.3) **are restricted during the treatment period** as well.

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

- Medications that are NOT allowed 8 hours prior to MCCB assessment (i.e. randomization visit, Visit 6/ week 12 and Visit 11/ week 26/ eEoT) is done:
  - Antihistamines with prominent sedative side effects
  - Anticholinergics
  - Benzodiazepines
  - Other sedative medication
  - Short-term use of opioids for pain, cough or diarrhea
- Anticholinergics
  - The total daily dose must not exceed 1 mg benztropine twice daily or equivalence.
  - If patients are being treated with more than 1 anticholinergic (including OTCs), the total daily dose still must not exceed 1 mg benztropine twice daily equivalence (e.g., diphenhydramine is an antihistamine with anticholinergic component).
  - Patients should remain on stable anticholinergic dose, unless absolutely necessary to adjust for medical reasons.
  - Screening period can be used to reduce anticholinergic use to maximum 1 mg benztropine twice daily in total, if clinical situation allows per investigator's judgement.
- Antihistamines
  - Patients taking sedative antihistaminic medication should be on a stable dose not exceeding daily recommended dose per label in the country.
- Opioid maintenance therapy or opioid-replacement for opiod dependence (e.g methadone) is not allowed during the trial period.
- CYP3A4 sensitive drugs with NTI (e.g., fentanyl, cyclosporine) are not allowed during treatment with Iclepertin. List is included in the ISF.

Permitted therapies include:

1. Non-systemic use (topical, inhalation or nasal administration) of antihistaminics and anticholinergics is allowed.
2. Short-term opioid therapy up to 4 weeks per time, for example with cough syrup or pain killer, is allowed (except fentanyl).
3. The CYP3A4 sensitive drugs without NTI have decreased levels of exposure when given concomitantly with Iclepertin; investigators should assess if dose adjustments and/or monitoring of the underlying disease is clinically required for patients who are taking such drugs (for a list of CYP3A4 without NTI sensitive drugs please refer to the ISF)
4. Vaccination with COVID -19 vaccines is permitted as per local public health recommendations.

4.2.2.2 Restrictions on diet and lifestyle

Diet and lifestyle restrictions listed under the **eligibility criteria** (Section 3.3.3) **are restricted during the treatment period** as well.

It is not recommended that patient donates blood during the study.

Effects of Iclepertin on driving abilities have not been tested so far. It is recommended that subjects exercise caution when driving or operating machinery during the treatment period.

Entering or modifying a smoking-cessation program during the treatment period could negatively impact efficacy read-outs and should be avoided if possible.

4.2.2.3 Contraception requirements

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

Acceptable methods of birth control for this trial include:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion or ligation
- Vasectomised sexual partner with documented absence of sperm

- Complete sexual abstinence when this is in line with the preferred and usual lifestyle of the patient (note: periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception)

Male patients and their female partners:
There are no specific contraceptive requirements for male participants and their female partners.

4.3 TREATMENT COMPLIANCE

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

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

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

If the number of doses taken is not between 80-100%, site staff will explain to the patient the importance of treatment compliance and determine the reason(s) for deviation and document these in the source and eCRF.
Adverse Events related to the human abuse potential of Iclepertin should be reported and managed as per the investigator´s judgement.

In addition to compliance calculation, medication adherence will be monitored via [redacted] app. Please refer Section 5.6.2 for more details.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

- **MATRICS Consensus Cognitive Battery (MCCB)** will be used to evaluate the effects of Iclepertin on cognitive functions.
  MCCB comprises 10 tests, which assess 7 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition [R13-2347; R13-2373].

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

  Table 5.1: 1 MCCB tests and cognitive domains

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

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

- **Schizophrenia Cognition Rating Scale (SCoRS)** is a 20-item interview-based assessment of cognitive deficits and the degree to which they affect day-to-day functioning. Each item is rated on a 4-point scale. Higher ratings reflect a greater degree of impairment.
  The 20 items of the SCoRS specifically assess cognitive functioning, and 19 of these items align with the seven MCCB cognitive domains as follows:
  - Memory: 4 items
  - Learning: 2 items
  - Attention: 3 items
  - Working Memory: 2 items
  - Problem Solving: 3 items
  - Processing/Motor speed: 2 items
  - Social Cognition: 3 items

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

  The SCoRS rater integrates information from separate patient and study partner interviews to generate a total score. In addition, the patient, study partner and interviewer (rater) will provide a global rating score at each post-baseline visit and the interviewer (rater) will provide a change score at the eEoT visit.

  Placebo Control Reminder Script (PCRS) [R20-4054]: The PCRS is a brief psychoeducational tool designed to mitigate placebo responses. A trained rater reads a brief passage about factors that have been linked to elevated placebo responses (e.g., misunderstandings about the purpose of a placebo treatment condition, unwarranted expectancies regarding treatment benefit) and encourages patients to attend to these factors.
  The patient and study partner are then asked to describe the content of the script in his/her own words. The procedure takes approximately three minutes to complete.

- **Virtual Reality Functional Capacity Assessment Tool (VRFCAT)** will be used as an electronic Functional Capacity measure for this study. The VRFCAT is a virtual reality shopping trip performed on a tablet. The task has several linked and sequential scenarios, including matching a recipe to the content of kitchen cabinets, preparing a shopping list, taking the correct bus, shopping efficiently, and catching the correct return bus. These tasks are performed in a fixed sequence. There are multiple forms of the VRFCAT and in this protocol different versions will be assigned according to the study visit. All data are collected through the computer or tablet.

  Prior to the performance of the task, a brief tutorial version of the VRFCAT is administered with a short recipe. This tutorial needs to be administered to all participants, regardless of their statements regarding computer familiarity.

  Once the task is launched it operates itself continuously until the end of the procedure. As with all electronic assessments, the tester will be required to remain vigilant in order to

ensure that the participant is continuously engaged in the task. The task takes approximately 30 minutes to complete.

The VRFCAT was developed to improve clinical trials by detecting functionally meaningful improvements in patients' everyday lives. Data generated in this trial will support validation of this test as a functional outcome measure for future clinical trials.

- **Tower of London (Executive Functions/Reasoning and Problem Solving):** Subjects are shown two images presented on opposite sides of the tablet screen. Each image shows a different configuration of 3 colored balls arranged on 3 pegs. The subject is required to accurately determine the total number of times the balls in one picture would have to be moved in order to make the arrangement of balls identical to that of the other opposing picture, while employing the standard rules employed in tower tests (balls are moved one at a time and balls on top of other balls must be moved first). Eight alternative forms are available. The outcome measure is the number of correct responses. The administration time is about 7 minutes.

- **Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS)** is a patient reported outcome (PRO) under development in accordance with FDA guidelines (2009) for recording patients' subjective experience of CIAS. The questionnaire contains 28 items and generally takes about 5-15 minutes to complete. The PRECIS asks the patient to assess their own subjective experience of CIAS over the past week, covering 6 domains Memory (6 items), communication (4 items), self-control (3 items), executive function (4 items), attention (6 items), and sharp thinking (3 items). Two additional items assess the overall degree of bother associated with all domains. Questions are answered via a 5-category Likert scale, with higher scores corresponding to worse patient experience (1=not at all/not at all hard, 2=a little bit/a little bit hard, 3=somewhat/somewhat hard, 4=quite a bit/quite hard, 5=very much/very hard), e.g. "Overall, in the past week, remembering where I put things (for example, my keys, phone, glasses, or other items) was…". The Total Score is derived by calculating the simple average score of the first 26 items. Domain scores can be calculated as simple average of the items that fall into the respective domain. If there are more than 7 missing items out of the first 26, a total score should not be calculated. For number of missing items allowed for each domain scores see Table 5.1:2. Table 5.1:2 lists the 28 items of PRECIS, their corresponding domain, and the minimum number of non-missing items required for each domain.

Table 5.1: 2 PRECIS items, domains and missing data allowance

Domains	Item descriptions	Item numbers	Minimum number of non-missing items required (per domain)
Memory	Remembering what I was supposed to do, Remembering where I put things, Remembering what I wanted to say, Remembering what someone was saying, Remembering how to get to someplace, Remembering what I was about to do	1, 2, 3, 4, 5, 6	3
Communica-tion	Coming up with something to say, Interacting with people I don't know well, Explaining myself, Finding words to say what I mean	7, 8, 9, 10	3
Self-control	Keeping things from slipping out, Stopping to think before saying or doing, Stopping saying or doing wrong	11, 12, 13	3
Executive Function	Planning ahead for an event, When someone changed plans, Coming up with solutions to problems, Figuring out new ways to do things	14, 15, 16, 17	4
Attention	My mind drifted off, Got distracted by things going on, Hard to focus on something, Thinking about things repetitively, Thoughts were racing, Thinking was unclear, cloudy, foggy	18, 19, 20, 21, 22, 23	3
Sharp thinking	Thinking was not as fast as others, When tired, thinking slowed, Thoughts were blocked	24, 25, 26	3
NA	Overall bother in the past week	27	
NA	Overall bother if thought stay the same	28	

- **Clinical Global impressions – Severity (CGI-S)** is a one-item evaluation completed by the clinician on the patient's severity of cognitive impairment. The CGI-S is rated ordinal from 1 to 4 (none, mild, moderate, severe). Ideally, the same investigator or site staff should assess CGI-S at all visits (refer also to section 6.2.1 for additional requirements).

- **Clinical Global impressions – Change (CGI-C)** is a 5-point scale (much better, a little better, no change, a little worse, much worse) used to assess the change of the patient´s status from start of the treatment and is completed by the clinician.

- **Study Partner Global Impression of Severity (SPGI-S)** is similar to CGI-S but completed by the study partner.

- **Study Partner Global Impressions of Change (SPGI-C)** a similar question as the CGI – C but completed by the study partner.

- **Patient Global Impressions-Severity (PGI-S)** is a 4-point scale with similar response categories as CGI-S, which requires the participant to rate the severity of their own symptoms.

- **Patient Global Impressions-Change (PGI-C)** measures a patient's belief about the efficacy of treatment. PGI-C is a 5-point scale with similar response categories as CGI-C, depicting a

patient's rating of overall improvement since started taking the study medication and is completed by the patient.

- **Health-related quality of life (HRQoL)** will be assessed using the **EQ-5D-5L** instrument at the visits indicated on the FlowChart. EQ-5D-5L is a standardized instrument for use as a measure of health outcome. It is a generic measure, rather than disease-specific, and is therefore applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile from which a single index value for health status is derived, and a visual analogue scale (VAS) rating.
  EQ-5D-5L is designed for self-completion by patients. The EQ-5D-5L self-report questionnaire consists of 2 pages comprising:
  - The descriptive system (5 dimensions of health: mobility, self-care, usual activities, pain/ discomfort, anxiety/ depression). Each dimension comprises 5 levels (no problems, slight/moderate/ severe problems, extreme problems, or unable to perform the health dimension)
  - The EQ visual analogue scale (VAS) which records the patient's self-rated health status on a vertical graduated (0 – 100) VAS

  A patient can self-administer the EQ-5D-5L in a few minutes, and the investigator (or designated site-personnel) should ensure that the patient has access to a quiet area at the site where he/she can complete the descriptive system and VAS. In instances where a patient is having difficulty deciding upon a response, he/ she should select the option that fits best. Investigators (or designated site-personnel) should not scrutinize responses to individual items. Instructions to patients will be included in the questionnaire [R12-1920].

- **Sheehan Disability Scale (SDS)**
  The Sheehan is a brief self reported tool assessing the functional impact of patients with psychiatric disorders. The patient rates on 3 items the extend to which work/school, social life and home life or family responsibilities are impaired by his or her symptoms on a 10 point analog scale [R20-1844]. Higher scores indicating greater functional impairment. It also comprises two additional items assessing days lost and days unproductive, respectively ('On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities?', 'On how many days in the last week did you feel so impaired on your symptoms, that even though you went to school or work, your productivity was reduced?).

- **Caregiver burden and caregivers' health-related quality of life:** Caregiver burden and caregivers' health-related quality of life will be collected from those study partners that are informal (unpaid) caregivers. Assessments will be voluntary, using the EQ-5D-5L and Schizophrenia Caregiver Questionnaire (SCQ).
  - **The Schizophrenia Caregiver Questionnaire (SCQ)**. The SCQ was developed to provide a comprehensive assessment of the impact of caregiving for an individual with schizophrenia [1,2]. It is a 32-item questionnaire with a recall period of 4 weeks ('during

the past 4 weeks'), utilizing a 11-point numerical rating scale from 0 to 10 for all items, with higher scores indicated greater impact. Scores of the SCQ are obtained by a sum of the recoded item scores, linearly transformed to a 0 to 100 range. The questionnaire comprises a 'Humanistic impact' supra-domain composed of a global score (17 items) and four subdomain scores ('Physical' (3 items); 'Emotional' (6 items); 'Social' (3 items); 'Daily life' (5 items)) and eight other domain scores related to the caregiving role ('Exhaustion with caregiving' (2 items); 'Feeling alone' (1 item); 'Patient Dependence' (2 items); 'Worries for the patient' (3 items); 'Perception of caregiving' (2 items); 'Financial dependence of the patient' (1 item); 'Financial impact of caregiving' (1 item); 'Overall difficulty of caregiving' (1 item)). Accordingly, 9 multi-item scores and 4 single item scores can be derived, and reliability and validity have been confirmed [R20-3808].

- **Socioeconomic status** will assess patient's working or employment status and housing situation (living alone, with family, etc.). A dedicated page to assess socioeconomic status will be available in the eCRFs.
- **HCRU** will collect details about hospitalizations, home hospitalizations, ER visits due to psychotic symptoms, and other non-study physician visits.

5.2 ASSESSMENT OF SAFETY

- **Positive and Negative Syndrome Scale (PANSS)** will be used to evaluate broad psychopathology associated with schizophrenia disease state.

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

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

- **Extrapyramidal Symptoms (EPS) will be assessed using 3 scales:**

  - The Simpson Angus Scale (SAS) is a performance scale that measures drug-induced parkinsonism symptoms. The rater asks the patient to perform 10 tasks and rates responses on a scale of 0-4 (normal to severe). It consists of one item measuring gait (hypokinesia), six items measuring rigidity and three items measuring glabella tap, tremor and salivation, respectively. A total score of 0-40 is calculated (or scale score can be calculated by dividing the total by 10 to give a score between 0 and 4).

  - The Abnormal involuntary movement scale (AIMS) records the occurrence of tardive dyskinesia (TD) in patients receiving antipsychotic medications. The AIMS test is used to

detect TD and to follow the severity of a patient's TD over time. These items are also scored from 0 (= normal/healthy) to 4 (= severely affected). The scores are summed to give an overall score of the involuntary movements. It assesses tardive movement disorders.

- The Barnes Akathisia Rating Scale (BARS) is a rating scale that is administered by the investigator to assess the severity of drug-induced akathisia. The BARS is the most widely used rating scale for akathisia. The BARS is scored as follows: Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9. In addition, Global Clinical Assessment of Akathisia is rated from 0-5.

- **Columbia Suicidality Severity Rating Scale (C-SSRS)**

  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 C-SSRS interview may be administered using a tablet device.

  Subjects who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in about 3 minutes. Subjects with significant suicidal ideation or behavior may require up to 10 minutes to answer all relevant questions. This assessment should be conducted early in the visit. At the conclusion of each assessment, the site will have access to the C-SSRS results. The results include the findings for suicidal ideation, intensity of ideation, suicidal behavior, and lethality / medical damage (for actual suicide attempts only).

  The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered first at screening (Visit 1) (using the ‘Baseline / Screening’ version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to screening. The lifetime history of suicidal ideation and behavior will also be recorded.

  After screening (Visit 1) the assessment ‘since last visit’ will be performed at each clinic visit (‘Since Last Visit version’). The investigator is to review/ consider the C-SSRS results for plausibility and clinical relevance. Doubtful results may be repeated or results may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit (if the investigator did not administer the C-SSRS leading to the positive report), and/ or is to consult a psychiatrist if considered necessary.

For any positive suicidal ideation (type 1 to 5) or suicidal behavior, the rater must document additional details in the comment fields in the C-SSRS in Pathway.

If there is any new suicidality or increase in suicidality, please comment on the clinical significance and any additional follow-up actions that may be performed in the eCRF.

If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated and followed up as deemed necessary. The C-SSRS may be repeated at an unscheduled visit at the investigator's discretion.

C-SSRS results will be reported in terms of AEs as described in Section 5.2.6.1.4.

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

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

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

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

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

Patients do not have to be fasted for the blood sampling for the safety laboratory.
All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the lab manual in the ISF.

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

The central laboratory will send reports to the investigator (except for blinded Hb related parameters, for further details refer to Section 4.1.5.1 and Section 5.2.6.4). Laboratory values that are out of range should be commented on lab report printouts and evaluated by the investigator for clinical significance.

Clinically significant abnormal laboratory results should be reported by the investigators in the eCRF either on baseline condition (from Visit 1 test) or on AE page (from subsequent visits test). Please refer to Section 5.2.6.

Clinically relevant abnormal laboratory test results will need to be followed per investigators judgment, until normalization or stabilization or until an alternative explanation has been found.

Safety lab may be repeated for any or all lab parameters specified in the protocol, at any time point during the study, per investigators discretion.

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

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

The site should not use a local laboratory to assess the Haematology parameters unless clinically justified.

Table 5.2.3:1 Safety laboratory tests

Category	Test name	
Haematology Panel A *(Refer Section 5.2.6.4)*	Haemoglobin (Hb) Haematocrit (Hct) MCV, MCH, MCHC RDW	Red Blood Cell Count/ Erythrocytes Reticulocyte Count Reticulocyte index
Haematology Panel B	White Blood Cells/ Leukocytes Diff. Automatic (manual if diff. automatic is abnormal) - Neutrophils - Eosinophils - Basophils - Monocytes - Lymphocytes	Platelet Count/ Thrombocytes Total iron binding capacity (TIBC) Serum ferritin Serum iron Folate Vitamin B12
Chemistry	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Bilirubin Total, fractionated if increased Creatine Kinase (CK) CK-MB – only if CK is elevated C-Reactive Protein Gamma-Glutamyl Transferase (GGT/γ-GT) Lipase Amylase Cholesterol, total Triglycerides Lactic Dehydrogenase (LDH)	Calcium Sodium Potassium Glucose HbA1c Urea (BUN) Creatinine Estimated Glomerular filtration rate (eGFR) – using the CKD-EPI equation**** Protein, Total TSH* Prolactin*
Pregnancy test (females only)	Human urine chorionic gonadotropin** Serum Beta hCG, Qualitative (Only if human urine chorionic gonadotropin is positive)	
Urinalysis (quantitative)	Urine creatinine	
Urinalysis (Qualitative)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen	Urine Bilirubin Urine blood Urine pH Leukocyte esterase
Urine Drug Screen *** **(Preliminary and confirmatory testing)**	Amphetamines Barbiturates Cannabis Cocaine	Methadone Opiates PCP (Phencyclidine)

*The following lab parameters will not be determined at each study visit:

- TSH – only at Visit 1
- Prolactin – only at Visit 2 and EOT/ eEoT

** To be done at the site with the kit provided by the central lab.

*** Patients will be considered drug screen positive, if the confirmatory test is positive. Re-test is permitted at

visit 1a (refer to Section 3.3).
****The eGFR will be derived from the serum creatinine value, age, sex and race using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [R12-1392]. The race must be collected because the CKD-EPI equation uses race as an adjustment factor and therefore it is required for accurate estimation.

5.2.4 Electrocardiogram

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

The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the patient's medical file if there is no validated and certified e-medical record for ECG data.

Additional ECGs may be collected by the investigator for safety reasons. Clinically relevant findings noticed at Visit 1 should be reported as baseline condition.

Clinically relevant abnormal findings noticed after Visit 1 will be reported as AEs and followed up and/or treated locally until normal or stable condition.

All ECGs will be transmitted electronically to the central ECG vendor for centralized and independent evaluation tThe vendor will provide a report to the site. Abnormalities detected during this centralized ECG evaluation will not necessarily qualify as an AE. Decisions on eligibility for the trial are the responsibility of the investigator. Abnormalities detected in central evaluation must be reviewed by the investigator and if considered clinically significant reported as baseline condition if identified at Visit 1 or as adverse event if identified at or after Visit 2. All clinically relevant abnormal findings will be managed as medically appropriate, per investigators clinical judgment

5.2.5 Other safety parameters

Assessment of disease state:

PANSS will be used to evaluate the disease severity. Refer to Section 5.2. In addition investigator may use CGI-S and his/her clinical judgment for assessing schizophrenia worsening/ relapse.
Schizophrenia worsening (i.e., deterioration of chronic residual symptoms): Fluctuation in the severity of symptoms is common and should be managed and reported as per the clinical judgment of the investigator. Adjustment of background medication is allowed when necessary. In such cases, schizophrenia worsening must be reported as adverse event per the clinical judgment of the investigator.

Schizophrenia Relapse (acute episode): If **severity** of schizophrenia symptoms fulfils the criteria of relapse (acute episode), investigator must report relapse as adverse event.
Definition of relapse for this program is: Increased level of care (such as hospitalization, home hospitalization, emergency room (ER) visit due to psychotic symptoms) due to worsening of psychotic symptoms / increased PANSS per investigators judgment.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

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

5.2.6.1.3 AEs considered “Always Serious”

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

The latest list of “Always Serious AEs” can be found in the EDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.

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

5.2.6.1.4 Suicidal Risk assessed by the C-SSRS

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

For each instance of suicidal ideation type 1, 2 or 3 after start of the trial, the investigator is to decide based on clinical judgement whether it represents an AE as defined in the protocol. If this

is considered as AE, then it must be reported as SAE, using SAE form and eCRF AE page, as this is listed on the "BI always serious adverse event list".

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

5.2.6.1.5 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs:

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

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist".
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.

5.2.6.1.6 Intensity (severity) of AEs

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

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

5.2.6.1.7 Causal relationship of AEs

Medical judgement 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 reduced).

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- **For patients *who* roll-over to the extension trial:**
  - From signing informed consent onwards until first dose of trial medication in the extension trial: all AEs (serious and non-serious) and all AESIs. Updates to

concomitant therapy should also be included until first dose of trial medication in the extension trial.
Note: Updates for SAEs and/ or AESIs ongoing at the time of rollover to the extenstion trial, must be also updated in parent trial, in addition to the extension trial, as long as the data base of parent trial is not locked. On SAE form, updates for events reportable on SAE form with onset in parent trial are only reported into the parent trial.

- **For patients who <u>do not</u> roll-over to the extension trial:**
  - From signing the informed consent onwards until the 28 days (F2 visit) after the end of treatment visit: 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 new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related 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 (see section 5.2.6.2.2), but not on the CRF.

- **For patients who permanently discontinue trial medication prematurely:**
  - From signing the informed consent onwards until the 28 days (Follow-up 2 visit) after the early end of treatment visit: all AEs (serious and non-serious) and all AESIs.

  - **From Follow-up 2 visit up to the individual patients' planned end of Trial (i.e. 26 weeks/visit 11):** Until the individual patient's planned end of trial, the investigator must report
    - Treatment related SAEs / AESIs
    - Following regardless of causal relationship
      - Anaemia
      - SAEs from C-SSRS assessments
      - Any occurrence of cancer
      - Deaths/ fatal AEs

  - **After the individual patient's planned end of trial (i.e. 26 weeks/ completion of visit 11):** The investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related 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 (see section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the 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 immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process 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 send 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. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.6.3 Ocular AE

Before administration of study medication at Visit 2, site staff will remind patients to report "any unusual visual perception they may experience".

During the study, if a patient reports a change in perception or any ocular AE, site staff must record the patient's verbatim description in the source documents and report it in the same way in the eCRF (and SAE form, if applicable).

A local ophthalmology assessment will be required for all ocular adverse events. The ophthalmologist will act as a consultant to the investigator and may offer advice on the proper management and treatment for the reaction as per standard of care.

5.2.6.4 Haemoglobin and Anaemia

To reduce bias on efficacy assessments, starting at visit 2 until the end of trial, **Haematology Panel A parameters** (refer table 5.2.3:1) will be blinded to the site and to the sponsor.

Sites will be alerted if the following occurs:

- **Alert 1:** Hb decrease > 20 g/L (2 g/dL) compared to baseline value
- **Alert 2:** The Hb value is **below** the normal reference range
- **Alert 3:** Hb value fulfils the criteria to withdraw the treatment (refer to Section 3.3.4)

An independent third party will review both **haematology panels** parameters throughout the trial. In addition, the independent DMC will review unblinded safety data on a regular basis throughout the study.

Scenarios and Actions:

Alert 1:

- Patients may continue on the study medication.
- Both haematology panels should be performed at the next visit (or earlier, per investigator's judgement). Both haematology panels should be repeated at subsequent visits until alerts are no longer triggered or once the end of trial has been reached.

Alert 2:

- Patients may continue on the study medication.
- Both haematology panels should be performed at the next visit (or earlier, per investigator's judgement). Both haematology panels should be repeated at subsequent visits until alerts are no longer triggered or once the end of trial has been reached.
- The investigator should further evaluate the patient status and report the AE "Anaemia" based on investigators clinical judgment. Once Alert 2 is no longer trigged, the investigator may evaluate whether or not the AE "Anaemia" is resolved.

For Alert 1 and/or 2, patients can be rolled over to the extension study. Details on monitoring of ongoing adverse event "Anaemia" in the extension study will be provided in 1346-0014 study protocol (c33088336).

Alert 3:

- **Stop study medication.** Refer to Section 3.3.4.2.
- Report as an AE "Anaemia"
- Both haematology panels should be performed at the next visit (or earlier, per investigator's judgement). Both haematology panels should be repeated at subsequent visits until alerts are no longer triggered or once the end of trial has been reached.
- Patient should be referred to a specialist for further management.
- Patients are not eligible for the extension trial.
- These patients will undergo follow up per Section 5.2.6.2.1 AE collection and Section 6.2.5.

Note: The Investigator may consider further management once any Alert is triggered.

5.2.6.5 AE for assessment of potential abuse liability

To assess whether Iclepertin has abuse potential, investigators are required to provide a detailed description of specific types of AEs. Detailed information should be recorded in the source documents and eCRF and if applicable, on the SAE form. A list of AEs for assessment of potential abuse liability will be provided as part of ISF.

5.2.6.6 Monitoring of adverse events after stopping of study medication

Patients who are not rolling over to the extension trial should be closely monitored during the safety follow up period to assess AEs after stopping of study medication.

5.2.6.7 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure

during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

If a patient becomes pregnant, please also refer to section 3.3.4.2**.**

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Trough samples will be collected as specified in Flow Chart before dosing the patient. Patients will be asked to:

- record the time of drug intake on three consecutive days before PK visits
- record if the drug intake was with or without food on the three consecutive days before PK visits
- record the time when they had last meal intake on the day of the visit with PK sampling.

5.3.2 Methods of sample collection

For quantification of drug plasma concentrations of Iclepertin, venous blood will be collected using a pre-labelled potassium ethylenediamine-tetraacetic acid (EDTA) containing blood drawing tube at the times indicated in Appendix 10.1. A detailed description of sample collection and handling is provided in the laboratory manual.

Plasma samples may be retained for 6 months after the final clinical trial report has been signed.

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

Banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flow Chart.

Blood will be drawn for DNA, Plasma and Serum banking purposes.

Any analyses on DNA or plasma/serum samples will not be reported in main CTR.
Samples will be collected only in countries where all applicable local regulatory and ethics approvals have been obtained for biobanking.

5.6 OTHER ASSESSMENTS

5.6.1 Speech sample collection

Speech analysis has emerged as new potential marker of abnormal mental conditions as for instance cognititive imparement in disorders like Schizophrenia. Speech analysis includes various evaluations of language as e.g. semantic coherence or syntactic complexity.

For use in future exploratory investigations, voluntary speech samples will be collected after separate optional speech sampling informed consent has been given in accordance with local ethical and regulatory requirements in participating countries. Participation in the speech sampling is not a prerequisite for participation in the trial.

Speech samples, along with related information on communication and mental state, will be collected with a tool on the tablet computer. The tool leads the participant through a set of speech elicitation tasks designed to assess motor and cognitive function as well as affect. Acoustic and language-level features will be extracted from the speech data and will be used to examine changes in speech and language features for each participant over time. These data may be

combined with data from other trials of psychiatric indications to explore possible association between speech parameters and clinical parameters.
Speech collection will occur at the time points indicated in the Flow Chart. Instructions for recording are provided in a speech analysis procedures manual, filed in the ISF

Note: speech sample collection may not be available in all countries at initiation and therefore will be implemented as soon as it is available and approved by regulatory authorities and ethic committees in respective countries.

Speech analyses will be analysed independently by a vendor and reported in a separate report.

5.6.2 Medication Adherence and Reminder System

Because non-compliance with medication is a significant challenge in Schizophrenia trials, this study will use a medication adherence monitoring platform for all participants in the study. All patients must consent to use the [redacted] app at screening. If a randomized patient on treatment refuses to continue to use the app, the patient will be allowed to continue in the trial.
The Platform is provided on the [redacted] smartphone application and uses artificial intelligence to confirm medication ingestion. Built-in reminders and a communication system **allow real-time intervention in case of missed doses**. Use of the platform is foreseen for all subjects in the study to reinforce the proper dosing schedule and improve data integrity.

Registration in the [redacted] platform
In most countries, the platform may be downloaded as an app on the participant's personal smartphone. If a participant does not own a smartphone or prefers not to use his/ her personal smartphone, one of the backup provisioned devices should be provided. In some countries, all participants will use a provisioned device.
Participants should be registered in the platform during screening visit and begin confirming appropriate compliance to their background antipsychotic treatment/s to ensure stability prior to randomization. At visit 2, participants will begin using the platform to monitor study drug intake and continue to log their background antipsychotic use.

Ongoing use and monitoring of medication adherence
- Participants should use the application to record each intake of study medication throughout the trial, both at home between visits and during the visits when study drug is taken at the site.
- Site personnel should regularly check the dashboard to ensure consistent medication adherence throughout the study. In cases of missed doses or pending data, site personnel should follow up with the participant as soon as possible to assess the reason for non-adherence and reinforce the importance of complying with the study drug dosing schedule. If the participant reports that a dose was taken but not logged in the app, site personnel should reclassify this dose to "site reported" using the dashboard.

- Participants who are consistently non-compliant with study medication should be discussed with the sponsor.

Monitoring of background antipsychotic treatment
Participants using a daily oral antipsychotic should be registered in the platform during screening to confirm stability of their background antipsychotic prior to randomization. Participants will be asked to confirm that they have taken their background antipsychotic treatment.

Data Privacy and Security in the [redacted] platform
The [redacted] platform is compliant with all applicable privacy and data security laws; data is captured, processed, and analyzed in a compliant manner as outlined in each local informed consent form

5.6.3 Verification of current and past research study status with [redacted]

Duplicate enrollment and protocol violations are risk factors for poor quality data and safety concerns. These issues may result in increased placebo rates and failed clinical trials. Each subject, in this study, must have their current study status checked by utilizing the [redacted] system. **This is a mandatory process for countries that have not opted-out by a local amendment**.

Following proper informed consent and after issuing a study subject number, each subject will be checked in the [redacted] database, as indicated in the Flow Chart. Partial identifiers will be utilized. This will include checking a valid form of picture ID when available. The first 3 letters of the first and last name will be entered along with the middle initial, DOB, Sex, and last 5 digits of that ID. If the research subject is a Verification Success they may proceed in the study. Verification Failures will not be permitted to screen without sponsor approval.

The duplicate patient check will be performed only after approval is received in accordance with local regulations.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

The scheduled measurements are appropriate to see drug induced changes in physical examination, vital signs, ECG and standard laboratory values. The primary and secondary efficacy endpoints and safety endpoints are standard and accepted for evaluation of safety and tolerability of an oral drug, and they are widely used in these kind of studies. The period of 26 weeks of treatment with Iclepertin is deemed appropriate to see a change in cognitive function in schizophrenic patients.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Study procedures have to be completed according to the Flow Chart. All patients should adhere to the visit schedule as specified in the Flow Chart including time windows for rescheduling. Preferably the visits should be conducted in the morning.

If any visit has to be rescheduled, subsequent visits should follow the original visit schedule calculated from randomization (Visit 2). The trial medication kits contain sufficient medication to allow for these time windows.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 General requirements

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

- **The MCCB should be done as the first efficacy assessment preferably in the morning (depending on the sleep cycle of the patient), followed by VRFCAT, ToL and SCoRS.**
- All other assessments can be completed per the convenience of patient and site at all respective visits.
- It is very important to have the MCCB done at approximately the same time of day for each individual patient throughout the trial. The MCCB assessments at Visit 6 and (e)EoT Visit must be started at approximately the same time of the day as MCCB assessment at Visit 2 (+/- 60 minutes). In case this cannot be adhered to, then the visit should be rescheduled within the allowed visit window.
- Assessment of each rating scale should preferentially be done by the same rater for a given patient throughout the study period. However, for MCCB and VRFCAT, the consistency of time of day is more important than the consistency of the rater.
- The global impression anchor scales (CGI-S/CGI-C and/or PGI-S/PGI-C and/or SPGI-S/SPGI-C) should be assessed after SCoRS at the respective visits when they are scheduled. Similarly, patients should complete PGI-S/PGI-C after PRECIS is completed at the respective visits when these measurements are scheduled. If qualified, the SCoRS rater should preferably perform the CGI-S/CGI-C.
- The CGI rater should base their assessment after review of information about that patient at that visit for CGI-S or since start of treatment for CGI-C including the SCoRS interview.
- To prevent bias on SCoRS rating, raters of SCoRS should remain blinded to the patient's performance on both MCCB and VRFCAT and MUST be different from the person adminstring MCCB and VRFCAT.

- During the MCCB assessments and throughout the visit, patients are allowed to take short breaks as needed, in the judgement of the rater/investigator.
- In case of patient experiences acute episode of schizophrenia (relapse), all efficacy assessments MUST be rescheduled (even if outside the visit window) until patient stabilizes, per investigators judgment. All safety assessments including PANSS, C-SSRS should be conducted, if possible.
- It is the responsibility of the Principal Investigator at the site to ensure that all site staff members are properly trained on all trial procedures and training documentation is filed in the ISF.
    - In addition, the site staff members who are administering the scales must be trained and certified.
- Vital signs and ECG should always be measured before any blood samples are taken. For further details on how to collect ECG, please refer to Section 5.2.4, for details on vital signs measurement, please refer to Section 5.2.2.
- Any abnormal condition of clinical significance identified, during physical examination, vital signs, 12 lead ECG, laboratory assessment or any other medical assessment should be recorded as a baseline condition (if noted at screening)/ adverse event (if noted during treatment or follow up period), as applicable.
- Safety lab and/ or drug screen test (urine), may be performed more frequently based on investigator discretion or if required locally.
- Patients do not have to come fasted for any trial visits.

Study partner requirements:

- The study partner should remain constant throughout the trial period, however in exceptional circumstances, a change of study partner will be allowed.
- Input from study partners will be required on the assessments indicated in the Flow Chart.
- In-person ratings are preferred whenever possible. However, if the study partner is not available for in-person ratings, telephone interview is acceptable. The telephone interview with the study partner must be conducted within the visits window indicated in the Flow chart for which study partner input on SCoRS, PANSS and SPGI-S/C is required.

For study partners who also fulfil the criteria of a caregivers:

- Study partners **who are also caregivers** will be asked to complete the EQ-5D-5L and SCQ. Please refer to Appendix 10.2 for definition of study partner vs. caregiver.

- For caregiver assessments, in person visit is preferred. However, if not possible, the caregiver may come on another day to fill-in the EQ-5D-5L and SCQ questionnaires – this should be as close to the visit as possible, preferably within the study visit window.

COVID-19 specific instructions:

- During the COVID-19 pandemic, there might be situations when patients already in the study might not be able to come to the site for the scheduled visit. This might be due to restrictions set by authorities or by the investigator site/institution, because the patient is quarantined, or because of any patient specific situation that the investigator judges as being not safe for the patient to come to the site. For details on potential modifications of the trial conduct related to the COVID-19 pandemic, please refer to Appendix 10.3.

6.2.2 Screening period

Screening Period (Visit 1 and Visit 1a, as applicable)

- A signed trial informed consent form must be obtained from the patient before either the patient or the study partner performs any study related procedure.

  A signed informed consent form must be obtained from the study partner before performing any study related procedure by the study partner. Visit 1 may be performed over multiple days within the screening period. If visit 1 procedures are performed on multiple days, each individual assessment or procedure must not be conducted over 2 different days (for example, the entire MCCB must be performed on one day). All visit 1 procedures must be completed before completing visit 1a. The patient is recorded on the enrolment log and registered in the IRT system as a screened patient.
- **Duplication check:** the patient IRT number and identifiers will be recorded on the vendor portal to confirm that the patient is not participating in another clinical trial. Screening can only continue after [redacted] provides confirmation. The investigator will receive email confirmation from the duplication check vendor that the patient is currently not participating in another trial in their database. Once email is received the site can continue screening.
- Please refer to the general requirements in section 6.2.1.
- **Drug of abuse testing:** During screening, the investigator should highlight to patients the importance of not taking drugs of abuse during the study, and that the urine drug screen will be repeated periodically throughout the trial. Patients should also be informed that they cannot participate in the trial if they have a positive urine drug screen (see further the relevant exclusion criterion in Section 3.3.3).
- The MCCB scoring sheets must be sent to the vendor [redacted] as soon as possible. The Screening MCCB T-score is required for randomization via the IRT at visit 2.

- **Eligibility Assessement:**
  - Once all screening procedures are complete (including laboratory results are received), all data collected should be reviewed against the eligibility criteria.
  - If the patient is eligible, the patient should be contacted to schedule next visit (Visit 2).
  - If the patient is not eligible (i.e. if they are considered a screen failure), they must be registered as a screen failure in IRT.
- **Rescreening:** Patients who fail screening may repeat the screening period once after discussion between investigator and sponsor. Please see Section 3.3 for further details regarding re-screening.

6.2.3 Treatment period(s)

- The randomized treatment period is from Visit 2 to EoT or (e)EoT Visit.
- Please refer to the general requirements in Section 6.2.1.
- Please refer to Appendix 10.3 for guidance in case of any exceptional circumstances. Sites should consult with sponsor before making any modifications.
- At Visit 2, and during the treatment period, patients should be reminded to take the trial drug as instructed, see Section 4.1.4.
- At Visit 2, and as needed throughout the treatment period, patients should be reminded about the importance of not taking drugs of abuse during the trial, and that the urine drug screen will be repeated periodically throughout the trial.

6.2.3.1 Randomization (Visit 2)

- It should be ensured that all Visit 1 and Visit 1a procedures have been successfully completed.
- MCCB is to be done before any other efficacy assessments.
- Study procedures for Visit 2 can be split into 2 sequential days, in which case:
  - The MCCB and VRFCAT must be performed on the first day.
  - The remaining assesments can be done per the convienence of the patient and site, either on day 1/ day 2.
  - To reduce burden on study partner, it is recommended to perform PANSS and SCoRS on the same day.
  - In case of a split visit, the second day will be day of first study drug intake.

- Biobanking sample, for patients who have signed the optional Biobanking consent form, should be collected before the intake of the first dose of study medication (refer to Section 5.5.1).
- **The MCCB overall T-score from the visit 1 (screening) is required for randomization at visit 2.**
    - In case that screening MCCB T-score is not available at visit 2, site may postpone this visit by maximum of 2 weeks.
- Patient eligibility must be confirmed before the patient is randomized in the IRT. Intake of the study medication must be done after the patient has completed all of the other visit 2 assessments.
- First intake of trial drug will be done on site using the [redacted] medication adherence monitoring app and under supervision by trial staff.
- The first two medication kits will be dispensed and will contain sufficient trial drug for 28 days (21 treatment days plus 7 days reserve). For further information refer to Section 4.1.4.
- At each clinic visit, patients should be reminded not to take study medication AT HOME on the morning of the visit. At each visit, patient will take medication AT THE CLINIC using [redacted] under supervision by trial staff.

6.2.3.2 Visit 3 to Visit 10

- Pre-dose PK blood samples will be collected during the treatment period as per the Flow Chart. Patients should not take trial medication before coming to the clinic on visit days. Refer to Section 5.3 and Appendix 10.1 for more details.
- Patients should be instructed to bring all trial medication (used and unused kits/ packaging including blisters) with them to these clinic visits.
- Sufficient trial drug for 28 days (21 treatment days plus 7 days reserve), as assigned by IRT, will be dispensed at each visit.
- Visit 6 can be split into 2 sequential days, in which case:
    - MCCB and VRFCAT should be performed on the first day;
    - The remaining assesments can be done per the convienence of the patient and site, either on day 1/ day 2.
    - To reduce burden on study partner, it is recommended to perform PANSS and SCoRS on the same day.
- At Visit 10, patients will be instructed to take the last dose of study medication on the day before the EoT Visit. In case the EoT Visit is split into 2 sequential days, the last dose of study medication should be taken on the day before the first day of the split visit.

6.2.3.3 End of Treatment (EoT) Visit - For Treatment completers

- Trough PK samples will be collected at the EoT Visit (approximately 24 hours after the last dose) for all patients who have not permanently stopped taking the study medication.
- The final MCCB assessment at the EoT Visit must be performed after the patient completes the 26 week treatment period.
- The EoT Visit can be split into 2 sequential days, in which case:
    - The MCCB and VRFCAT must be performed on the first day.
    - The remaining assesments can be done per the convienence of the patient and site, either on first day or the second day of the EOT visit.
    - To reduce burden on study partner, it is recommended to perform PANSS and SCoRS on the same day.
- Termination of trial medication eCRF pages will be completed.

6.2.4 Follow up of Treatment completers

6.2.4.1 Trial completers rolling-over to the extension trial

Patients who complete the 26 weeks treatment in 1346-0011 and are willing to participate in the open label extension trial with Iclepertin 10mg (c33088336):

- The patient completing the 26 week treatment period will be considered as treatment and trial completer. If the patient rolls over into the extension trial at the EOT visit (preferred option), the Follow up period visits (14 and 28 days follow up visit) **do not have to be completed**. Termination of trial medication and trial completion eCRF pages will be completed with same visit date.
- The patient will start participation in the open label extension trial with Iclepertin 10mg (c33088336).
    - This extension study is conducted under a separate trial protocol and patients will need to provide consent to participate in the extension trial.
    - These patients may enter the extension trial (Visit 1) either (preferably) on the day of EOT or at the latest 2 weeks after the EOT visit (i.e. Follow up 1 timepoint including the applicable time windows).
    - If patient decides to roll over between day 1- 7 after EOT, no safety laboratory assessment needs to be done unless medically required.
    - If patient decides to roll over between day 8 – 14 after EOT, the assessments according to Follow up visit 2 shall be completed instead of Follow-up visit 1.
    - If patients decide, at the latest 2 weeks after the EOT visit, not to roll-over to extension, please follow the instructions in Section 6.2.4.2.

- Further details will be provided in the 1346-0014 protocol (c33088336).

6.2.4.2 Treatment completer not rolling over to extension:

- Patients who completed 26 weeks treatment but are unwilling to participate in the open label extension trial with Iclepertin 10mg (c33088336), safety follow up visits (14 and 28 days follow up visit) will be completed as planned.
- After completing 28 days of follow up, the patient will be considered a trial completer. Trial completion eCRF pages will be completed.
- Patients should continue to take their background therapy for schizophrenia, as prescribed by the investigator or treating physician.

6.2.5 Early Permanent Treatment Discontinuation and further follow up

Every effort should be made to collect data in all randomised patients. This includes randomised patients who never took the study medications and patients who permanently discontinued study drug.

6.2.5.1 Early Permanent Discontinuation from Treatment

- If a patient permanently discontinues the study medication, an eEOT visit must preferably be performed within 7 days after the last dose of study medication. It is extremely important that patient should be encouraged to complete at least the MCCB, SCoRS and VRFCAT assessments. The termination of trial medication eCRF page must be completed with the reason for discontinuation of treatment.
- The eEoT Visit can be split into 2 sequential days, in which case:
  - The MCCB and VRFCAT should be performed on the first day;
  - PRECIS should not take place immediately after MCCB, to avoid bias
  - The remaining assesments can be done per the convienence of the patient and site, either on first day or the second day of the eEOT visit.
  - To reduce burden on study partner, it is recommended to perform PANSS and SCoRS on the same day.
- After the eEOT visit patients should complete the safety follow-up visits and continue with scheduled trial visits and assessments until the planned end of the trial for that patient unless they withdraw consent to participate in the study.
  - Refer to the Retention Guide in your ISF for further instructions.
- If it is not possible to attend all visits, a phone contact should occur at the scheduled visit time points. It is vital to explain to these patients the importance of continued trial participation.

- When discussing options for continued trial participation, sites must present the first option to the patient and discuss this option thoroughly before presenting the next option for follow-up.
- **Patients should be encouraged to choose the most rigorous follow-up regimen they are willing and able to comply with. The investigators should inform these patients that they will be allowed to change this regimen later if needed.**
- **Patients may choose to re-start trial medication intake at any time during their planned treatment period as long as there is no safety concern in the opinion of the investigator.**

Table 6.2.5.1: 1 Follow-up of patients who prematurely discontinue the study treatment*

Early D/C Option 1	Continue to conduct regularly scheduled study visits as per protocol and prioritize the collection of the efficacy endpoints, at least for the primary, key secondary and secondary efficacy endpoints
In case patient does not agree to option 1, then present **Early D/C Option 2**	Focus on key efficacy endpoints MCCB, SCoRS, VRFCAT (the minimum at least MCCB) and safety** assessments per Flow Chart.
In case patient does not agree to option 2, then present **Early D/C Option 3**	Collect safety** data: • at scheduled study visit time points **or** • as agreed with the patient **or** • at least at planned EOT or EOT +28 days, whichever is longer

* Dispense and administer IMP, IMP compliance check, [redacted] related activities, PK Sampling, biobanking sampling do not need to be performed in patients who have permanently stopped taking the study drug.
** Safety data may be collected from the patient, or a person designated by the patient (e.g., family, spouse, partner, legal representative, or physician etc…) or through review of patient's medical information from alternative sources (e.g., doctor's notes, hospital records, etc.). Refer section 5.2.6.2.1 AE Collection: For patients who permanently discontinue trial medication prematurely.

6.2.5.2 **Safety Follow up:** Patients who prematurely discontinue treatment

- Follow up Visits will be conducted 14 and 28 days after the early EoT visit.
- In case the Follow-up visits are completed earlier than the planned timepoints by mistake, then a repeated follow-up visit on or after 28 days post early EOT needs to be performed.
- AEs that are ongoing at the last Follow-up Visit should be followed up until they are resolved, have been assessed as “chronic” or “stable”, or no further information can be obtained or deemed reasonably followed up by the investigator. Refer Section 5.2.6.2.1 AE Collection: For patients who permanently discontinue trial medication prematurely.
- Refer to ISF for follow up post 28 days (Follow-up 2 visit) up to the planned end of Trial Period (i.e. 26 weeks).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary efficacy objective is to assess the absolute difference in adjusted mean change from baseline to Week 26 in MCCB overall composite T-score (cognition) for once daily oral treatment with Iclepertin 10mg QD as compared with placebo in patients with CIAS. The key secondary efficacy objectives are to assess the absolute difference in adjusted mean change from baseline to Week 26 in SCoRS interviewer total score and adjusted total time T-score in VRFCAT between Iclepertin 10mg QD and placebo. Intercurrent events will be addressed using a strategy that differs depending upon the nature of the intercurrent event.

The treatment effect for the following treatment policy is of interest: patients remain on randomized treatment for the duration of the trial unless an exacerbation or acute episode or an event considered to be drug-related interrupts or discontinues treatment. Changes in background medication or non-pharmacological intervention are allowed.

Estimation will assume that the policy is followed by all randomized patients. All measurements obtained for patients while on this policy are therefore relevant for the estimation of the primary estimand, while measurements obtained after a deviation from this policy are not relevant for the estimation of the primary estimand.

The following intercurrent events are considered to form part of the treatment policy being assessed and hence subsequent measurements are included in the primary analysis of the endpoint:

- Change in background medication (e.g. antipsychotics, etc)
- Change in non-pharmacological therapy (e.g. cognitive therapy, any kind of psychotherapy, nicotine withdrawal therapy, diet, etc)
- Exacerbation or acute episode which results in interruption or early termination of treatment
- Investigator assessed drug-related adverse events which lead to early termination of study medication
- Protocol-defined drug withdrawal due to treatment, e.g. haemoglobin decrease, concomitant medications with CYP3A4 substrates
- Change in study partner in the assessment of functional capacity, e.g. SCoRS

All other intercurrent events are considered to represent breaks from the treatment policy and therefore confound estimation of the treatment effect of interest. Such intercurrent events would include, for example, early termination of treatment due to reasons unrelated to treatment (e.g. consent withdrawal, incarceration, somatic illness like stroke, cardiovascular events, etc, hospitalization due to somatic illness). Measurements after these intercurrent events are excluded from the primary analyses.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The hypothesis testing strategy is a gatekeeping procedure [R20-0199] with strong control of family-wise type I error rate at one-sided 0.025 as depicted in Figure 7.1: 1. The first family consists of the superiority hypothesis test (H1) of the primary endpoint. The second family consists of the superiority hypothesis tests (H2 for SCoRS and H3 for VRFCAT) of the two key secondary endpoints. The third family consists of the superiority hypothesis tests (H4 for Tower of London and H5 for PRECIS) of the two secondary endpoints. The overall family-wise type I error rate is controlled at one-sided alpha of 0.025. Let α_1, α_2 and α_3 denote the controlled one-sided alpha rate allocated at the beginning of Family 1, Family 2 and Family 3 and $\alpha = \alpha 1 = 0.025$. The observed one-sided p-values from each hypothesis test in each family are denoted as p_1, p_2, p_3, p_4, and p_5.

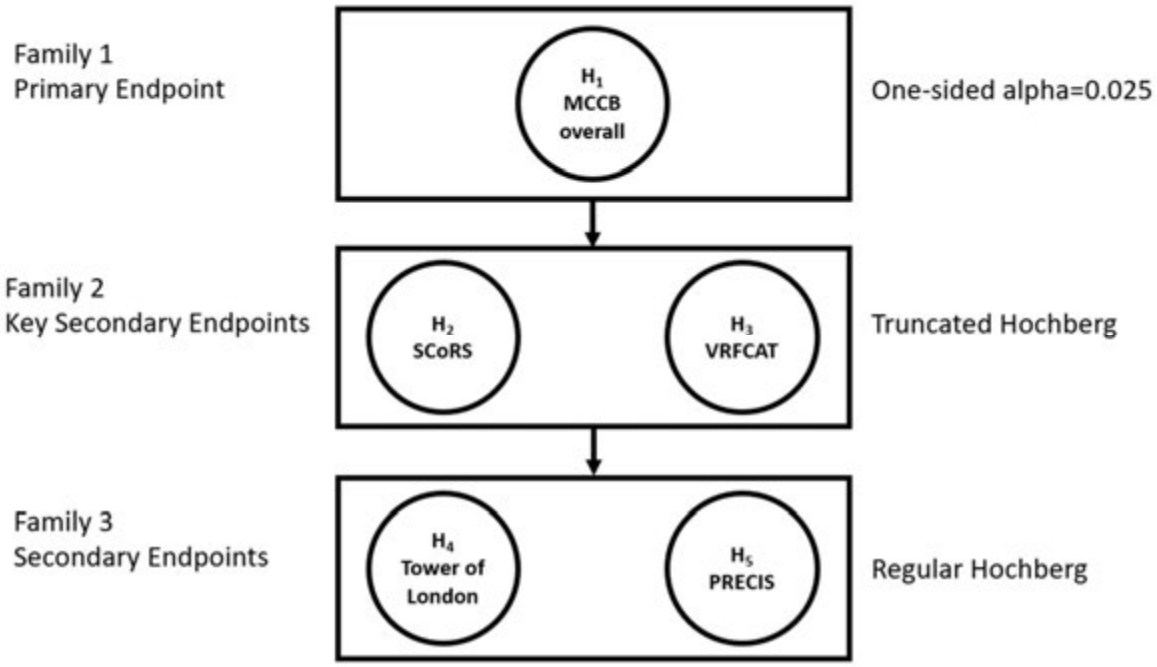

Figure 7.1: 1 Gatekeeping procedure of the hypothesis testing strategy

a) First family: Superiority test of the primary endpoint, change from baseline to Week 26 in MCCB overall composite T-score

(1) $H_{0,1}$: The adjusted mean change from baseline to Week 26 in MCCB overall composite T-score in Iclepertin 10mg QD is worse than or equal to that in placebo;

versus

$H_{A,1}$: The adjusted mean change from baseline to Week 26 in MCCB overall composite T-score in Iclepertin 10mg QD is better than that in placebo.

The primary objective of this pivotal phase III trial will be achieved if $H_{0,1}$ is rejected at the one-sided alpha of 0.025 level and this trial is considered a success. Family 1 serves as a parallel gatekeeper for Family 2. If $H_{0,1}$ is not rejected at one-sided alpha of 0.025 level, then $\alpha_2 = 0$ and no formal hypothesis tests in the second and third families will be conducted.

After $H_{0,1}$ is rejected, the full family-wise type I error rate of one-sided 0.025 will be passed on to the hypothesis tests in the second family (i.e. $\alpha_2 = 0.025$ one-sided) for which a truncated Hochberg approach [R97-0605] will be used with a truncation parameter γ. Based on our simulation results, we choose $\gamma = 0.2$ for this trial.

b) Second family: Superiority tests of the two key secondary endpoints

(2) $H_{0,2}$: The adjusted mean change from baseline to Week 26 in SCoRS interviewer total score in Iclepertin 10mg QD is worse than or equal to that in placebo;

versus

$H_{A,2}$: The adjusted mean change from baseline to Week 26 in SCoRS interviewer total score in Iclepertin 10mg QD is better than that in placebo.

(3) $H_{0,3}$: The adjusted mean change from baseline to Week 26 in adjusted total time T-score in VRFCAT in Iclepertin 10mg QD is worse than or equal to that in placebo;

versus

$H_{A,3}$: The adjusted mean change from baseline to Week 26 in adjusted total time T-score in VRFCAT in Iclepertin 10mg QD is better than that in placebo.

If both p_2 and p_3 are $< \alpha_2*(1+\gamma)/2$ (one-sided), then both hypothesis tests are statistically significant and the one-sided type I error of 0.025 will be passed on to the third family, i.e. $\alpha_3 = 0.025$.

If the maximum of p_2 and p_3 is $\geq \alpha_2*(1+\gamma)/2$ (one-sided), then the smaller of the two p-values will be tested at one-sided alpha of $\alpha_2/2$ and the corresponding hypothesis test is statistically significant if the remaining p-value is $< \alpha_2/2$ (one-sided). In this case as only one of the two key secondary efficacy endpoints is statistically significant, the remaining alpha of $\alpha_3 = \alpha_2*(1-\gamma)/2$ will be passed on to the third family.

If neither $H_{0,2}$ nor $H_{0,3}$ in the second family are rejected, then no alpha will be passed onto the third family, i.e. $\alpha_3 = 0$ and none of the hypothesis tests in the third family is controlled for family-wise type I error and hence will not be considered as formal hypothesis tests.

Family 2 serves as a parallel gatekeeper for Family 3 which means that the formal hypothesis testing procedure will proceed to Family 3 if at least one of the two null hypotheses ($H_{0,2}$ and $H_{0,3}$) is rejected in Family 2. If one or both of $H_{0,2}$ and $H_{0,3}$ in Family 2 is rejected, then the remaining family-wise type I error rate α_3 will be passed on to the hypothesis tests in the third family for which a regular Hochberg method will be used.

c) Third family: Superiority tests of the two secondary endpoints

(4) $H_{0,4}$: The adjusted mean change from baseline to Week 26 in the T-score of the number of correct responses on Tower of London in Iclepertin 10mg QD is worse than or equal to that in placebo;

versus

$H_{A,4}$: The adjusted mean change from baseline to Week 26 in the T-score of the number of correct responses on Tower of London in Iclepertin 10mg QD is better than that in placebo.

(5) $H_{0,5}$: The adjusted mean change from screening to Week 24 in PRECIS total score in Iclepertin 10mg QD is worse than or equal to that in placebo;

versus

$H_{A,5}$: The adjusted mean change from screening to Week 24 in PRECIS total score in Iclepertin 10mg QD is better than that in placebo.

If the maximum of p_4 and p_5 in Family 3 is $< \alpha_3$ which is the one-sided alpha passed down from Family 2 to Family 3, then both $H_{0,5}$ and $H_{0,6}$ are rejected. Otherwise, if the maximum of p_4 and p_5 is $\geq \alpha_3$ which is the one-sided alpha passed down from Family 2 to Family 3, then the smaller p-value will be compared with $\alpha_3/2$, and the corresponding null hypothesis is rejected if the p-value is $< \alpha_3/2$.

All further endpoints are not under the type-I error control, and hence, all analyses are considered exploratory.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following patient analysis sets are defined for this trial:

- Randomized Set (RS): includes all patients who signed informed consent and were randomized into the trial, regardless if a patient was treated with trial medication. The RS is used for efficacy analyses and patients in RS are analysed under the randomized trial medication. Patients randomized in error and discontinued from the study before the start of trial medication will be excluded from the RS.

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

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

In general, baseline values are the measurements taken prior to the first administration of trial medication at randomization (Visit 2), or Visit 1a if no measurements are planned at Visit 2, (see Flow Chart). Further details will be provided in the TSAP.

7.2.2 Primary endpoint analyses

The primary analysis of the primary efficacy endpoint uses the Randomized Set. Subjects will be analysed according to the stratum to which they actually belong (not necessarily the stratum they are randomized to, and regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before ranodmisation and is therefore consistent with the regulatory guidance. Intercurrent events are handled as specified in Section 7 above and missing data as a result from the strategy (including both actual missing outcomes and excluded outcomes) will be handled using a mixed effects model with repeated measures (MMRM) under the assumption of missing at random. Forchange from baseline to Week 26 in MCCB overall composite T-score, a restricted maximum likelihood (REML) based approach using MMRM will be conducted to compare the adjusted mean between Iclepertin 10mg QD vs. placebo. The MMRM includes the fixed categorical effects of treatment at each visit, fixed categorical effect of the stratification factor using the screening MCCB overall composite T-score, and the fixed continuous covariates of baseline MCCB overall composite T-score at each visit. Subject is treated as random effect. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-subject measurements.

The statistical model is:

$$y_{ijkm} = \beta_j S_i + \tau_{jk} + \varphi_m + e_{ij}, \text{ where } \boldsymbol{e}_i \sim N_T(0, \Sigma),$$

where

y_{ijkm} = response variable for subject i in stratum m at visit j receiving treatment k
$S_i =$ the baseline MCCB overall composite T-score of subject $i, i = 1, 2, \ldots$
$\beta_j =$ coefficient of baseline effect at visit $j, j = 1, 2, \ldots, T$
τ_{jk} = the effect of treatment k at visit $j, k = 1, 2$
φ_m = the effect of screening MCCB overall composite T-score stratum m for $m = 1, 2,$ and $\varphi_1 \equiv 0$ for stratum 1 of T-score < 30
e_{ij} = the random error associated with jth visit of the ith subject.
Σ = a $T \times T$ unstructured covariance matrix

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. The point estimates of the adjusted mean difference between treatment arms at each visit, together with the corresponding two-sided 95% confidence intervals and p-values will be presented. The primary treatment comparison will be the contrast between treatments at Week 26.

Procedures to follow if the MMRM analysis fails to converge will be described in the Trial Statistical Analysis Plan.

To assess the robustness of the primary analysis result, sensitivity analyses of the primary endpoint are planned in which the same strategy for handling intercurrent events as used for the primary analysis will be applied.

- For subjects who had early treatment termination due to exacerbation or acute episode or an event considered to be drug-related, missing data after the intercurrent event will be imputed through a reference-based multiple imputation method, i.e., using the observed off-treatment data from patients in the same treatment arm to impute the missing off-treatment data. All other missing data, e.g. missing on-treatment data or missing data after other intercurrent events, will be imputed using the observed on-treatment data from all randomized subjects in the same treatment arm.
- For all missing data, a reference-based approach using observed off-treatment data from the same treatment arm to impute missing data will be applied for multiple imputation. This would be a conservative approach to missing data assuming missing not at random.
- For all missing data, apply a jump-to-reference (J2R) method for multiple imputation, i.e. assume subjects in BI arm switch to the placebo arm distribution following the missingness. This would be a conservative approach to missing data assuming missing not at random.

After applying the above different multiple imputation methods for the missing data (including the "set-to-missing" data), an Analysis of Covariance (ANCOVA) model including the fixed effects of treatment, categorical effect of stratification factor using screening MCCB overall composite T-score, and baseline MCCB overall composite T-score will be fitted for the primary endpoint at Week 26. Rubin's rules will be applied to derive the single point estimates and the corresponding standard errors from the multiple imputations [R12-2094].

In addition, as a supplement to the strategy for handling the intercurrent events as used in the primary analysis and sensitivity analyses, we will conduct the following supplementary analyses for the primary endpoint:

- Handle all intercurrent events using treatment policy approach and then apply the same MMRM model as used in the primary analysis assuming missing at random.
- Handle all intercurrent events using hypothetical approach, i.e. censoring all data after the intercurrent event, and apply the MMRM model as used in the primary analysis assuming missing at random.
- Consider different strategies for handling intercurrent events, e.g. consider different set of intercurrent events to be handled using treatment policy, consider using while on treatment strategies.

More details on the sensitivity analyses and the supplementary analyses will be provided in the TSAP.

To address the COVID-19 pandemic or other potential public health crisis, BI plans to investigate logistical mitigation measures introduced for COVID-19 and develop statistical assessments accordingly, e.g. if the option for remote visits is introduced, BI will compare remote to in-person visits.

In addition, BI will summarize the prevalence of intercurrent events caused by COVID-19, e.g., COVID-19 infection as an AE; discontinuation of study treatment because of "administrative" reasons such as lack of availability of medical procedures and treatment, quarantine, travel restrictions, etc. The resulting intercurrent events lead to missing outcomes. Some patients may still be able to continue treatment if they have sufficient drug supply but may have missing outcomes because of missing evaluation visits. The proposed primary estimand and analysis strategies should already address COVID-19 related intercurrent events.

Currently, the following subgroup analyses are planned on P3 results:

- Baseline level of cognition (i.e., MCCB overall composite T-score)

As the same set of efficacy endpoints will be collected in three parallel pivotal phase III trials (1346-0011, 1346-0012, 1346-0013), BI plans to conduct random-effects and fixed effects meta-analyses using the pooled data from these three trials for the primary, key secondary and secondary efficacy endpoints. In these pre-planned meta analyses, the same gatekeeping procedure as planned for the hypothesis tests in each individual phase III trial will be conducted using a stand-alone family-wise type I error rate of one-sided alpha=0.025. These pre-planned meta-analyses will be conducted to provide a totality view of the data in the phase III clinical programs and to support the proposed indication.

7.2.3 Secondary endpoint analyses

For the two key secondary efficacy endpoints of change from baseline to Week 26 in SCoRS interviewer total score and adjusted total time T-score in VRFCAT, as well as the secondary efficacy endpoint of change from screening to Week 24 in PRECIS total score, the same strategy for handling the intercurrent events in the primary estimand analysis and a similar MMRM analysis used for the primary efficacy endpoint will be conducted to obtain the adjusted mean treatment effect between BI and placebo in terms of change from baseline to Week 26 (from screening to Week 24 for PRECIS total score). This MMRM model includes the discrete fixed effects of treatment at each visit, fixed categorical covariate of the stratification factor using the screening MCCB overall composite T-score, and continuous fixed effects for the corresponding baseline endpoint value at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure to model the within-subject measurements. Subjects will be considered as a random effect. The primary treatment comparison is the contrast between treatments at Week 26 (Week 24 for PRECIS total score). For change from baseline to Week 26 in the T-score of number of correct responses on Tower of London, an analysis of covariance (ANCOVA) model including treatment, stratification factor of screening MCCB overall composite T-score (< 30, ≥ 30), and baseline number of correct responses on Tower of London T-score will be fitted to the data.

Similar sensitivity and supplementary analyses as planned for the primary efficacy endpoint will also be conducted for the two key secondary efficacy endpoints.

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

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between the start of treatment and the end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 12 days after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

Frequency tables for all adverse events, protocol-specified adverse event of special interest (AESI), serious adverse event (SAE), adverse event leading to death, adverse event leading to discontinuation, investigator assessed drug-related adverse event and serious related adverse event will be generated for treatment-emergent adverse events. In addition, summary statistics and descriptive analyses will be conducted for other safety parameters that are assessed using dedicated scales, including suicidality as assessed by C-SSRS, disease severity as assessed by PANSS total score and changes over time on AIMS, SAS and BARS scales for EPS and related movement impairments.

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

regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

7.2.6 Other Analyses

Pharmacokinetic analyses

Plasma concentrations of Iclepertin at related time points will be analysed descriptivelyas further explained in Appendix 10.1.

7.2.7 Interim Analyses

No interim analysis is currently planned but safety will be monitored by an external and independent DMC.

7.3 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at the specific time points, even for subjects who terminated trial medication prematurely. If not specified otherwise, missing data are not imputed and remain missing. Potential outliers will be reported and analysed as observed.

For the primary estimand analysis of the primary efficacy endpoint using the mixed strategy for handling intercurrent events, if a subject misses a visit, the missing data will not be imputed. The MMRM analysis will handle missing data based on a likelihood method under the “missing at random” assumption.

MCCB endpoints

All imputations will be carried out separately for each study visit since there may be differences in test performance at different time points.

For the domains of Working Memory (consisting Letter-Number Span test and Wechsler Memory Scale 3rd ed. Spatial Span subtest) and the Speed of Processing (consisting Trail Making Test Part A, Brief Assessment of Cognition in Schizophrenia – Symbol Coding subtest, and Category Fluency test – animal naming), if only one of the tests consisting of a domain has missing value at a visit, the corresponding domain score can still be derived using the observed test raw score for that visit. If more than one of the tests consisting of a domain have missing value at a visit, the corresponding domain score is missing at that visit.
For the other five domains (Verbal Learning, Reasoning and Problem Solving, Visual Learning, Attention / Vigilance, and Social Cognition) which has only one test, if the test has missing value at a visit, the corresponding domain score is missing.

If a domain score is missing at a visit, the missing T-score of this domain can be imputed using the proprietary algorithm developed by MATRICS.

For baseline assessment, at least two-thirds of the cognitive domains (i.e., a minimum of five out of the seven domains for the MCCB overall composite score and a minimum of four out of the six domains for the MCCB neurocognitive composite score) need to be successfully assessed at baseline for it to be counted as a test occasion with non-missing baseline value.

For post-baseline assessments, at least half of the domains (i.e., a minimum of four out of the seven domains for the MCCB overall composite score and a minimum of three out of the six domains for the MCCB neurocognitive composite score) need to be successfully assessed to be considered a test occasion with non-missing value.

SCoRS endpoints

For the 20-item SCoRS assessment, if six or more of the 20 items have missing response, which includes the response of "N/A", for a subject at a visit, then the SCoRS total score for that subject at that visit is missing. If five or less of the 20 items have missing response, which includes the response of "N/A", for a subject at a visit, then the item with missing response will be imputed first with the average of the non-missing item values for the subject at the visit, and then SCoRS total score for the subject at the visit will be derived as the sum of the non-missing item values and the imputed item values.

PRECIS endpoints

The PRECIS scale consisted of 28 items, among which the first 26 items are coming from six domains, i.e., memory, communication, self-control, executive function, attention and sharpness of though, and the last 2 items measure overall degree of bother associated with all domains. For the aforementioned six domains, the maximum numbers of items allowed to be missing within each domain are 3, 1, 0, 0, 3 and 0, respectively, so that each domain would have at least 3 non-missing items. Within each domain, if the number of missing items exceed its allowable value, then the corresponding domain score would be considered missing, otherwise, the domain score is calculated as the average of the non-missing items scores under the domain. The PRECIS total score is calculated when not more than 7 items are missing overall, and the total score is calculated as the average of the non-missing item scores of the first 26 items.

A detailed description of the PRECIS items, the corresponding domains and the minimum number of non-missing items required for the domain scores is provided in Table 5.1:2.

Additional details on the handling of missing data will be specified in the TSAP prior to unblinding.

7.4 RANDOMISATION

Eligible subjects will be randomised in equal ratio to Iclepertin 10mg arm and the placebo arm. The randomisation will be implemented in blocks to achieve balanced allocation to each treatment arm. In addition, randomisation will be stratified by two factors: 1) the screening MCCB overall composite T-score (two strata: < 30, ≥ 30) with the cut-off values based on the characteristics of the MCCB overall composite T-score from historical data [R19-3841], and 2) participation in the ocular substudy (Yes, No).

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

7.5 DETERMINATION OF SAMPLE SIZE

Results from a phase II proof of clinical concept and dose ranging trial (1346-0009, c31477880) show the largest mean improvement of Iclepertin vs. placebo in change from baseline to Week 12 in MCCB overall composite T-score is about 2 points with the estimated standard deviation of approximately 5.8 at Week 12 (the estimated standardized effect size is about 0.35), and the largest mean improvement of Iclepertin vs. placebo in change from baseline to Week 12 in SCoRS interviewer total score is 1 point with the estimated standard deviation of approximately 5.5 at Week 12 (the estimated standardized effect size is about 0.2). For this phase III trial with a treatment duration of 26 weeks and considering a treatment effect under the proposed primary estimand framework (i.e. definition of intercurrent events and the corresponding handling strategies), we assume a standardized effect size of 0.35 in the sample size calculation for the primary and the two key secondary efficacy endpoints and also assess the power of the proposed sample size under different assumptions of the standardized effect sizes for the key secondary efficacy endpoints.

The method of the two-sample t-test with equal variances and equal n's using the software nQuery + nTerim 4.0 was used to calculate the sample size based on each of the primary and the key secondary efficacy endpoints individually. An effective sample size of 220 subjects per arm, 440 subjects in total, will detect a standardized effect size of 0.35 in the primary efficacy endpoint, or in any of the two key secondary efficacy endpoints individually, with 95% power under one-sided type I error rate of 0.025. With 220 subjects per arm and one-sided type I error rate of 0.025, a standardized effect size of 0.31, 0.286, 0.268, and 0.25 can be detected for each of the primary and the two key secondary efficacy endpoints individually with 90%, 85%, 80%, and 75% power respectively.

As a complex gatekeeping procedure is used for the hypothesis tests in this phase III trial and the controlled one-sided type I error rate for each hypothesis test depends on the result of other endpoints, it is very complicated, if not impossible, to derive the mathematical formula for the

power of each efficacy endpoints considered in the gatekeeping procedure. As a result, we conducted simulations to approximate the power for each efficacy endpoint (i.e. the probability of rejecting each null hypothesis) using the gatekeeping procedure under five different scenarios of the standardized effect sizes for each efficacy endpoint with the truncation parameter γ ranging from 0.2 to 0.9, 220 evaluable subjects per arm, one-sided family-wide type I error rate of 0.025, and 0.2 correlation among efficacy endpoints. We also approximate the probability of rejecting $H_{0,1}$ and one or both of $H_{0,2}$ and $H_{0,3}$ under the same five scenarios.

Simulation results as presented in Table 7.5: 1 show that with 220 evaluable subjects per arm, there is at least 95% power to detect an effect size of 0.35 in MCCB overall composite T-score, regardless of the effect sizes in SCoRS interviewer total score and the adjusted total time T-score on VRFCAT. Furthermore if the effect sizes in both key secondary efficacy endpoints are 0.35 (Scenario #1), then with 220 evaluable subjects per arm we have close to 90% power to detect such effect sizes and the probability of rejecting $H_{0,1}$ and one or both of $H_{0,2}$ and $H_{0,3}$ is close to 95%. If only one of the two key secondary efficacy endpoints has an effect size of 0.35 (Scenario #2), then with 220 evaluable subjects per arm we have close to 90% power to detect such an effect size and the probability of rejecting $H_{0,1}$ and one or both of $H_{0,2}$ and $H_{0,3}$ is 88.9%. If one of the two key secondary efficacy endpoints has an effect size of 0.3 but not the other key secondary efficacy endpoint (Scenario #3), then with 220 evaluable subjects per arm we have 78.6% power to detect such an effect size and the probability of rejecting $H_{0,1}$ and one or both of $H_{0,2}$ and $H_{0,3}$ is 79.6%. The simulation results also show that the truncation parameter γ ranging from 0.2 to 0.9 does not impact the marginal powers for the primary and the two key secondary efficacy endpoints much. Hence we choose $\gamma = 0.2$ as this gives the desired probabilities of success for the primary endpoint (>90%) and for the key secondary efficacy endpoints (about 80%), as well as larger probabilities of success for the two secondary efficacy endpoints under Scenarios #1, #2, #3 and #4 as compared with a larger γ value such as 0.8.

In summary with 220 evaluable subjects per arm, simulation results show satisfactory operational characteristics of the proposed gatekeeping procedure under Scenarios #1, #2 and #3 which are considered plausible for this phase III trial.

Table 7.5: 1 Probability of success for each endpoint under different scenarios of effect sizes from simulations

Efficacy Endpoints	**Primary:** MCCB Overall	**Key Secondary:** SCoRS total score	**Key Secondary:** VRFCAT	**Secondary:** Tower of London	**Secondary:** PRECIS	**Primary and Key Secondary:** reject $H_{0,1}$ and ($H_{0,2}$ and/or $H_{0,3}$)
Scenario #1 (assumed standardized effect sizes)	0.35	0.35	0.35	0.275	0.275	
Probability of rejecting null from 1000000 simulations	95.6%	89.3%	89.3%	75.2%	75.2%	94.6%
Scenario #2 (assumed standardized effect sizes)	0.35	0.1	0.35	0.2	0.275	
Probability of rejecting null from 1000000 simulations	95.6%	12.8%	88.6%	37.5%	60.9%	88.9%
Scenario #3 (assumed standardized effect sizes)	0.35	0.1	0.3	0.2	0.2	

Table 7.5: 1 Probability of success for each endpoint under different scenarios of effect sizes from simulations (con't)

Efficacy Endpoints	**Primary:** MCCB Overall	**Key Secondary:** SCoRS total score	**Key Secondary:** VRFCAT	**Secondary:** Tower of London	**Secondary:** PRECIS	**Primary and Key Secondary:** reject $H_{0,1}$ and ($H_{0,2}$ and/or $H_{0,3}$)
Probability of rejecting null from 1000000 simulations	95.6%	12.6%	78.6%	32.4%	32.4%	79.6%
Scenario #4 (assumed standardized effect sizes)	0.35	0.1	0.25	0.2	0.275	
Probability of rejecting null from 1000000 simulations	95.6%	12.5%	62.7%	30.0%	46.7%	65.2%
Scenario #5 (assumed standardized effect sizes)	0.35	0	0	0.2	0.275	
Probability of rejecting null from 1000000 simulations	95.6%	1.3%	1.3%	1.5%	2.0%	2.4%

With 220 evaluable subjects per arm, one-sided family-wise type I error rate =0.025, correlation between the endpoints = 0.2, truncation parameter $\gamma = 0.2$, and the gatekeeping procedure as shown in Figure 7.1: 1.

Based on the proportions of early treatment termination, subjects with missing data and missing data patterns as observed in our phase II trial 1346-0009 and anticipating higher proportions of early treatment termination based on previous literatures in long-term antipsychotic trials and more subjects with missing data in our phase III trial due to longer treatment duration, we project 30% to 40% subjects will prematurely terminate treatment in our phase III trial. Since BI will take every measure to collect all data at the planned visits from early dropout subjects, we anticipate 25% to 50% of these early dropouts will have efficacy outcomes collected after treatment termination and can be used in the analysis. Based on these estimations, we will apply

25% correction for missing data in the sample size calculation for this phase III trial. This gives a total number of 586 randomized subjects for the phase III trial, with 293 randomized subjects in each treatment arm.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following webpage: 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 finalisation of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

The investigator or delegate must give a full explanation to trial patients and study partner/caregiver based on the patient information form. A language understandable to the

patient and study partner/caregiver should be chosen, technical terms and expressions avoided, if possible.
The patient and study partner/caregiver must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's and study partner´s/caregiver´s own free will with the informed consent form after confirming that the patient and study partner´s/caregiver´s understands the contents. The investigator or his delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions and in accordance with all applicable local regulations.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.7.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. 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 at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source documents necessary for neurocognitive assessments (e.g. MCCB) will be provided to [redacted]. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The end of the trial is defined as the "individual patient's end of the trial of the last patient" (with individual patient's end of trial defined for patients not rolling over (here Follow-Up Visit 2) and for patients rolling over (day of first administration of study medication in the extension trial)
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.

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

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

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

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.

The DMC will evaluate safety data. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), 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 (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a central service evaluating ECG, a vendor for cognitive and neuropsychological assessments, a vendor for medication adherence monitoring, a vendor for duplication checks, a vendor for speech sample analysis and an IRT vendor will be used in this trial. Details will be provided in the respective manuals, available in the ISF.

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10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Table 10.1: 1 Time schedule for PK blood sampling

Visit	Day	Time Point	CRF Time/ PTM	Event
3	22	Preferrably within 30 min before drug administration	~0:30	PK Blood
4	43			
6	85			
8	127			
EoT	183	~1 day after last dose	~24:00*	
(e) EOT	NA	~as applicable after last dose	~24:00*	

*PK sample should be collected within the visit window. Precise collection timepoint must be captured in the eCRF.

10.2 DEFINITION OF STUDY PARTNER AND CAREGIVER

Who can be a study partner?	Who can be a Caregiver?
Study partner is any person who knows the patient well, has been capable of interacting with the patient on regular basis, preferably consistent throughout the study, either private or professional	Caregiver is a study partner who is taking informal (unpaid) care of the patient, which can be direct or indirect, including e.g. organizing or checking things for the patient, making phone calls, managing bills, arranging things and doing paperwork related to the patient, do shopping, cooking, cleaning, laundry, etc.
Every patient enrolled in the study must have a study partner	Patients do not need to have a caregiver but must have a study partner. Therefore, having a caregiver is optional.
Must sign study partner IC	Will be asked to complete additional questionnaires (SCQ, EQ-5D-5L) for caregiver assessment consent on study partner IC
The study partner must interact with the patient minimum 1 hour per week and, preferably, at least 2 times a week. At least one interaction per week should be in person.	As caregiver, study partner should spend an average of approximately 4 hours per week or more with care giving (direct or indirect, see above).
Don't need to be co-resident with the patients.	
Must have educational achievement of minimum 8th grade.	
Professional study partner (e.g. study nurse, social worker etc.) are allowed if not involved in administration of any of the protocol assessments.	Professional study partners cannot be caregiver as they are providing paid care.
Will provide input to SCoRS, PANSS, SPGI-S, SPGI-C. Study partners who are NOT caregivers, will not complete, EQ-5D-5L and SCQ to assess caregiver's Quality of life and the burden of caregiving	In addition to SCoRS, PANSS, SPGI-S, SPGI-C, the care-giver will complete EQ-5D-5L and SCQ to assess caregiver's Quality of life and the burden of caregiving.

10.3 POTENTIAL MODIFICATION OF TRIAL CONDUCT IN CASE OF RESTRICTIONS DUE TO COVID-19 OR OTHER EXCEPTIONAL CIRCUMSTANCES

In case of any restrictions during the COVID-19 pandemic or any other exceptional circumstances (e.g. emergency, natural disaster, patient specific situations, etc.) study conduct may need to be adjusted based on the investigator's discretion and agreed with the sponsor.

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

If on-site / clinic visits are not possible because the site/institution is limiting or restricting on-site visits due to COVID-19 (or any other exceptional circumstances), some of the visit procedures (including study partner contacts and assessments) can be done via home visit or telephone / video conference or locally (e.g. at a local lab, diagnostic centre, GP visit, etc.).

All COVID-19/exceptional circumstances-related deviations from the original schedule of visits and procedures will be documented, and the implications will be considered for the analysis of trial data.

The following contingency measures will be introduced to ensure patient safety and appropriate trial continuation based on a thorough benefit-risk assessment of treatment continuation versus early discontinuation, to be judged by the investigator on an individual patient level whereby patient safety always needs to be at the centre of decision-making (see Section 1.4).

The following study data should be collected/ reported during home and/or remote visit and/ or obtained locally:

- Birth control check (for women of childbearing potential)
- Safety and pregnancy test
- Vital Signs
- ECG
- Adverse Events
- Concomitant Therapies
- All scheduled scales and questionnaires (if possible)
- Study medication compliance check

Birth control check (for women of childbearing potential)/ pregnancy test

- The Investigator or designee must confirm with the patient (and study partner, if possible) that a reliable birth control method is being used consistently.
- Women of childbearing potential should have a pregnancy test performed if indicated in the Flow Chart or is required based on local regulations or investigator discretion.

Safety assessments:

- If home visits are possible, some assessments can be done at the patient's home (e.g. blood and urine samples, including PK samples, if applicable, can be collected and sent to the central lab, vital signs).
- If blood sampling or analysis by the central lab is not possible, safety lab analyses can be performed at a local laboratory. The results of the lab tests must be reported to the investigator who ensures medical review and proper documented in the eCRF.
- At a minimum the haematology panels should be done. Other safety laboratory tests may be performed at the Investigator's discretion.
- For the rare situations in which the safety laboratory test cannot be done, the investigator's reasoning and decision-making process must be documented in source notes at the site.

ECG:

- The ECG assessment can be done locally. The ECG report must be transferred to the investigator who ensures medical review and proper documentation in the eCRF.
- In rare situations in which the ECG(s) cannot be done, (even locally) and if ECG is normal or does not have any clinically significant findings at prior visits (per investigator's clinical judgment), the Investigator needs to consider the overall patient medical status, including premorbid conditions, before allowing the patient to continue on study treatment.
- In case ECG(s) cannot be done but the patients will be permitted to continue in the study and continue receiving the investigational product, this should be documented in the source documentation.

Study Medication Compliance check:

Patients can report and/or send photos of used study medication kits to the site staff, if needed and if possible. Medication kits including empty blister cards must to be return to the clinic. This may be done at the next visit, if in-person visits are permitted or arrangements can be made to have a courier retrieve the kit from the patient and return it to the site.
In addition, the site should monitor medication adherence through the [redacted] portal, if possible.

Direct-to-patient shipment of trial medication

If a patient is not able to come to a visit as planned but the investigator considers it favorable and safe for the patient to continue on trial medication, the trial medication can be shipped from site directly to the patient (if acceptable according to local laws and regulations). Such shipments require the use of a sponsor approved courier to the patient's home.

When scheduling visits every effort should be made to ensure a continuous supply of trial medication for the patient, whilst also taking into account that the next kit(s) of trial medication may need to be shipped from the site to the patient's home and, that medical pre-requisites should be performed and confirmed prior to shipment of new supplies.

Primary and secondary endpoint assessments: MCCB, SCoRS and VRFCAT

The MCCB, SCoRS and VRFCAT are designed to be conducted in person.
If it is not possible to conduct the visit in person, please contact the sponsor immediately.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		28 Oct 2022
EudraCT number **EU number**		2020-003760-11
BI Trial number		1346-0011
BI Investigational Medicinal Product(s)		Iclepertin
Title of protocol		A phase III randomized, double-blind, placebo-controlled parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-1)
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page and whole document
Description of change		BI 425809 replaced by Iclepertin
Rationale for change		Inclusion of the International Nonproprietary Names for Pharmaceutical Substances listed Iclerptin BI 425809
Section to be changed		Synopsis and section 2.1.3
Description of change		Key secondary efficacy endpoint VRFCAT updated to include T-score
Rationale for change		Clarified that the key secondary efficacy endpoint for the VRFCAT is the total adjusted time T-score.
Section to be changed		Flowchart and Abbreviations
Description of change		APP and PCRS added
Rationale for change		Administrative error / allow for consistency between section 5.1 and flow chart
Section to be changed		Flowchart footnotes
Description of change		Addition of footnote #18
Rationale for change		Clarify that study partner is required for SCoRS and PANSS interviews at least at Visit 2 and EOT
Section to be changed		Abbreviations
Description of change		Updates of CGI-S and CGI-C descriptions
Rationale for change		Administrative error
Section to be changed		Sections 1.4.2 and 5.2.6.3

Description of change		Change the requirement for ophthalmologic assessments to be performed only for moderate to severe vision related AEs.
Rationale for change		Request from FDA to have all ocular AEs assessed by an ophthalmologist.
Section to be changed		Sections 1.4.2 and 3.3.4.1
Description of change		Clarification that Paxlovid should not be used concomitantly with the study drug. Patients who require treatment with Paxlovid should temporarily discontinue the study drug.
Rationale for change		Paxlovid as a strong inhibitor of CYP3A may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Iclepertin is metabolised by CYP3a and therefore plasma concentrations of Iclepertin may increase significantly with concomitant Paxlovid use.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.3.2
Description of change		Inclusion criteria #5 updated to permit patients who are on 2 anti-psychotics that at least one has to be within the approved label dose range and the other must not exceed the maximum daily dose per local label.
Rationale for change		Clarification on the doses of background antipychotics that can be used
Section to be changed		Section 3.3.2
Description of change		Inclusion criteria #6 updated – removed reference to hypnotic load up to 0.25 mg brotizolam equivlance. Clarified that other psychoactive medications cannot exceed the maximum daily dose per local label.
Rationale for change		Clarification of the criteria to ensure that patients should not be taking both 1 mg lorazepam plus 0.25 mg brotizolam during the trial and that patients may take a lower dose of other psychoactive medication however the dose should not exceed the maximum daily dose per local label.
Section to be changed		Section 3.3.3

Description of change		Exclusion criteria #2 updated to exclude patients with epilepsy.
Rationale for change		Clarification that patients with epilepsy cannot be included
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria #8 updated to exclude use of esketamine as well as ketamine.
Rationale for change		Clarification
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria #10 updated to exclude only those patients who have previously been treated with iclepertin.
Rationale for change		Patients previously treated with Iclepertin cannot be enrolled however those patients who may have screen failed in another trial with BI 425809 could be considered for the CONNEX trial.
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria #11 updated including related footnote
Rationale for change		There are a number CNS acting medications that can be used to treat epilepsy but also other symptoms. Patients who take antiepileptics for treatment of epilepsy should be excluded however epileptics as monotherapy can be used for treatment of other conditions.
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria #18 updated to exclude patients who currently have anemia.
Rationale for change		Patients who had anemia in the past and currently do not have anemia could be enrolled.
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria #26 updated
Rationale for change		Clarification that list of ingredients can be found in the Investigator's Brochure
Section to be changed		Section 3.3.4
Description of change		Added guidance related to lost to follow-up patients and included a reference to retention guide.
Rationale for change		Ensure sites are aware of the procedures in case a patient is lost-to-follow-up
Section to be changed		Section 3.3.4.2
Description of change		Removal that patients need to be followed until EOT+28 days
Rationale for change		Clarification

Section to be changed		Section 3.3.4.2
Description of change		Addition of new reason for withdrawing (patients need to take restricted medications)
Rationale for change		For safety reasons, patients should not take prohibited medications during the treatment period however if these medications are necessary, then the patient should permanently discontinue the study drug.
Section to be changed		Section 4.2.2.1
Description of change		Removal of quetiapine example for sedative medications
Rationale for change		To reduce confusion since quetiapine is an antipsychotic and patients should continue to take their background antipsychotic as prescribed by their treating physician
Section to be changed		Section 4.2.2.1
Description of change		Clarify that short term use of opioids for pain, cough or diarrhea
Rationale for change		Clarification
Section to be changed		Section 4.2.2.1
Description of change		Addition of vaccination for COVID-19 in the permitted therapies
Rationale for change		Patients are permitted to receive a COVID-19 vaccination during the trial and in accordance with local public health recommendations.
Section to be changed		Section 5.1
Description of change		Addition of PCRS description
Rationale for change		Correction
Section to be changed		Section 5.1
Description of change		Corrected the number of items in the SCQ.
Rationale for change		correction
Section to be changed		Section 5.1
Description of change		Addition of reference to section 6.2.1 for CGI-S
Rationale for change		Clarification of expectations for this scale
Section to be changed		Section 5.1
Description of change		Addition of HCRU details that are collected.
Rationale for change		Clarification. These were previously described in section 2.2.2.1.1.
Section to be changed		Section 5.2
Description of change		Removal of number of items for AIMS
Rationale for change		Administrative error
Section to be changed		Section 5.2.3

Description of change		Confirmation that re-test is permitted at visit 1a in case patients are drug screen positive at Visit 1
Rationale for change		Clarification
Section to be changed		Section 5.2.6.4
Description of change		Addition of reference to section 3.3.4.2 in case of patient becomes pregnant
Rationale for change		Clarification
Section to be changed		Section 5.6.2
Description of change		Confirm that patients must consent to the use of [redacted] app but it won't be a reason for discontinuation if the patients to continue after randomisation
Rationale for change		The trial aims to retain as many patients as is possible to minimize the amount of missing data from randomized patients.
Section to be changed		Section 5.6.3
Description of change		Confirm that [redacted] will be used only for countries that have not opted-out by local amendment
Rationale for change		Clarification
Section to be changed		Section 6.2.1
Description of change		Removal of examples of scales that should be done by the same rater
Rationale for change		Ideally, all scales should be performed by the same rater whenever possible to minimize the amount of variability in the data created by rater differences.
Section to be changed		Section 6.2.1
Description of change		Description added for CGI-S requirements
Rationale for change		To clarify that the clinical global impression used in the trial should be based on the global impression including the patient's functioning based on the SCoRS assessment.
Section to be changed		Section 6.2.2
Description of change		Updated paragraph regarding patient and study partner informed consents
Rationale for change		Clarification that patient can start the trial procedure s after the patient has provided their written informed consent and even if the study partner informed consent is not yet signed.
Section to be changed		Section 6.2.3
Description of change		Addition of reference to appendix 10.3
Rationale for change		Ensure sites are aware of potential adaptations in case of exceptional circumstances

Section to be changed		Section 6.2.4.1
Description of change		Clarified which procedures patients need to complete if they roll-over into the extension trial after completion of the EOT visit
Rationale for change		Clarification.
Section to be changed		Sections 6.2.4.1 and 6.2.5.1
Description of change		Update of the different scenarios in case of early discontinuation and clarify re-start trial medication
Rationale for change		Clarification
Section to be changed		Section 7.2.1
Description of change		Addition of patients randomized by error and discontinued from the study before the start of trial medication
Rationale for change		Clarification Clarification that randomized set will exclude patients randomized by error and discontinued from the study before the start of trial medication
Section to be changed		Section 7.2.2
Description of change		Update of the statistical model
Rationale for change		Corrections
Section to be changed		Section 10.1
Description of change		Update of the day for visit 3
Rationale for change		Correction
Section to be changed		Section 10.2
Description of change		Revise wording to indicate that the caregiver will be asked to complete the additional questionnaires
Rationale for change		Clarification that caregiver will be asked to complete additional questionnaires (but not mandatory)
Section to be changed		Section 10.3
Description of change		Addition of exceptional circumstances in addition to COVID-19
Rationale for change		Ensure to include emergency, natural disaster, patient specific situations
Section to be changed		Section 10.3
Description of change		Clarification that study partner contacts and assessments can be also impacted
Rationale for change		Clarification
Section to be changed		Section 10.3
Description of change		Include analysis by the Central Lab in addition to blood sampling
Rationale for change		Include description in case the Central Lab is lockdown or if transportation routes to the central

		lab are disrupted such that samples cannot arrive in time to be analyzed.
Section to be changed		Section 10.3
Description of change		Include also secondary endpoints description in case of any exceptional circumstances
Rationale for change		Clarification that those assessments cannot be performed remotely as it would result in reduced quality.

11.2 GLOBAL AMENDMENT 2

Date of amendment		22 Dec 2022
EudraCT number **EU number**		2020-003760-11
BI Trial number		1346-0011
BI Investigational Medicinal Product(s)		Iclepertin
Title of protocol		A phase III randomized, double-blind, placebo-controlled parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-1)
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		1.3
Description of change		BI 425809 replaced by Iclepertin
Rationale for change		By mistake, replacement of "BI 425809" with the International Nonproprietary Names for Pharmaceutical Substances "Iclepertin" was missed in one place in this section in Global Amendment 1
Section to be changed		Table 1.4.2:1
Description of change		BI 425809 replaced by Iclepertin
Rationale for change		By mistake, replacement of "BI 425809" with the International Nonproprietary Names for Pharmaceutical Substances "Iclepertin" was missed in one place in this section in Global Amendment 1
Section to be changed		Figure 3.1:1
Description of change		BI 425809 replaced by Iclepertin
Rationale for change		By mistake, replacement of "BI 425809" with the International Nonproprietary Names for Pharmaceutical Substances "Iclepertin" was missed in one place in this section in Global Amendment 1
Section to be changed		4.2.2.1
Description of change		separate paragraph for Anticholinergics was created
Rationale for change		Formatting mistake in Global Amendment 1
Section to be changed		9.1
Description of change		Reference literature for Placebo Control Reminder Script was added
Rationale for change		By mistake, the reference literature was not added in this section in Global Amendment 1

11.3 GLOBAL AMENDMENT 3

Date of amendment		19 Sep 2023
EudraCT number **EU number**		2020-003760-11
BI Trial number		1346-0011
BI Investigational Medicinal Product(s)		Iclepertin
Title of protocol		A phase III randomized, double-blind, placebo-controlled, parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-1)
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page and synopsis
Description of change		Address of Coordinating Investigator
Rationale for change		Change of Address
Section to be changed		Flow Chart and footnotes
Description of change		Added footnote 21: C-SSRS may be repeated based on investigator discretion
Rationale for change		DMC recommendation
Section to be changed		5.2
Description of change		Reinforce documenting details for any positive suicidal ideation and to provide comments on the clinical significance and any additional follow-up action items. The C-SSRS may be repeated at an unscheduled visit based on investigator discretion.
Rationale for change		DMC recommendation
Section to be changed		Flowchart
Description of change		Substance use added to the flowchart
Rationale for change		To align with the CRF
Section to be changed		Compliance
Description of change		Clarification on calculation of compliance based on tablets removed from blisters
Rationale for change		To ensure the formula is consistent with the protocol text.
Section to be changed		Appendix 10.1
Description of change		Added “preferably within 30 minutes before dose to on treatment PK sampling timepoints, added “approximately” to other PK sampling timepoints.

		Added reminder that actual times are collected in the eCRF
Rationale for change		Clarification

11.4 GLOBAL AMENDMENT 4

Date of amendment		25 Jun 2024
EudraCT number **EU number**		2020-003760-11
BI Trial number		1346-0011
BI Investigational Medicinal Product(s)		Iclepertin
Title of protocol		A phase III randomized, double-blind, placebo-controlled, parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-1)
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page and synopsis
Description of change		Coordinating Investigator
Rationale for change		Former Coordinating investigator changed his affiliation and therefor is no longer available for this role as of 01 July 2024.

APPROVAL / SIGNATURE PAGE

Document Number: c32481549 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-05

Title: A phase III randomized, double-blind, placebo-controlled parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-1)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	03 Jul 2024 10:46 CEST
Author-Trial Clinical Pharmacokineticist		03 Jul 2024 13:34 CEST
Approval		03 Jul 2024 14:32 CEST
Approval		03 Jul 2024 17:55 CEST
Author-Trial Statistician		04 Jul 2024 16:56 CEST
Verification-Paper Signature Completion		04 Jul 2024 19:07 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed