Clinical Trial Protocol

Document Number:	c33088336-03	
EudraCT No. **EU Trial No.**	2020-003745-11	
BI Trial No.	1346-0014	
BI Investigational Medicinal Product(s)	Iclepertin (BI 425809)	
Title	An open label, single arm, extension trial to examine long-term safety of Iclepertin once daily in patients with schizophrenia who have completed previous Iclepertin Phase III trials.(CONNEX-X)	
Lay Title	A study to test long-term safety of Iclepertin in people with schizophrenia who took part in a previous CONNEX study	
Clinical Phase	III	
Clinical Trial Leader	[redacted] Phone [redacted] Fax [redacted]	
Coordinating Investigator	[redacted] Phone [redacted] Fax [redacted]	
Version and Date	**Version: 3.0**	**Date: 18 Sep 2023**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	15 Mar 2021
Revision date	18 Sep 2023
BI trial number	1346-0014
Title of trial	An open label, single arm, extension trial to examine long-term safety of Iclepertin once daily in patients with schizophrenia who have completed previous Iclepertin Phase III trials (CONNEX-X)
Coordinating Investigator	[redacted] Phone [redacted] Fax [redacted]
Trial site(s)	Multi-centre approximately 42 countries
Clinical phase	III
Trial rationale	The Iclepertin phase III program is comprised of 3 pivotal trials that will investigate the efficacy and safety of Iclepertin in patients with schizophrenia over 26 weeks of treatment. Trial 1346-0014 is a roll-over trial that will offer patients who have completed 26 weeks of treatment with Iclepertin or matching placebo, taken once a day, in any of the Iclepertin Phase III trials an opportunity to either continue or start to receive treatment with Iclepertin. Long-term safety data up to 1 year will be collected in this trial.
Trial objective(s)	The objective of this trial is to collect additional safety data in patients with cognitive impairment due to schizophrenia, who participated in and completed the 26-week treatment or matching placebo of one of the phase III clinical trial program for Iclepertin (trial # 1346-0011, 1346-0012, 1346-0013)
Trial endpoints	The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) throughout the extension study. Note: TEAEs are defined as all adverse events (AE) occurring between start of treatment in the extension trial and the end of its residual effect period (REP). AE that start before first drug intake in the extension trial and deteriorate under treatment during the extension trial will also be considered as 'treatment-emergent' The secondary endpoints are change from baseline in Clinical Global Impressions-Severity (CGI-S) to end of treatment (EOT) and Change from baseline in Hb to EOT.
Trial design	Multi-center, multi-national, open label, single arm extension trial in patients with cognitive impairment due to schizophrenia who have completed 26 weeks of treatment with 10 mg Iclepertin or matching

	placebo, taken once daily in one of the three phase III (CONNEX) parent trials (trial 1346-0011, 1346-0012 or 1346-0013).
Total number of patients entered	Apoximately 1400 patients
Number of patients on each treatment	Single arm 1400 patients on treatment with 10 mg Iclepertin
Diagnosis	Clinically stable outpatients with established diagnosis of Schizophrenia
Main in- and exclusion criteria	Main Inclusion criteria: • Clinically stable outpatients who have been diagnosed with schizophrenia (as per Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)). • Patients, who completed 26 weeks of treatment in the parent trial, must enter the extension trial: o Within 2 weeks the end of treatment visit in 1346-0011, 1346-0013 (i.e. Follow Up 1 timepoint including the applicable time windows). o At the end of safety follow up in 1346-0012 (within 7 days of visit Follow Up 6). • Have a study partner, defined as any person capable of understanding trial related procedures, with a minimum of 8th grade level of education, who knows the patient well, has been capable of interacting with the patient on a regular basis. Preferably be the same person throughout the study. Main Exclusion criteria: • Participant who developed DSM-5 diagnosis other than Schizophrenia or any condition that would prevent the patient from participating in the extension trial • Any suicidal behavior and/ or suicidal ideation of type 5 based on the C-SSRS in parent trial and up to and including Visit 1 of this study. • Patients diagnosed with moderate or severe substance use disorder • Haemoglobin- Hb drop below 100g/L (10g/dL) OR Hb decrease of 25% or more from baseline and is below lower limit of normal in parent trial (alert 3 from last measure Hb in parental trial) • Patients who have been diagnosed with hemoglobinopathies during the parent trial.
Test product(s)	Iclepertin
dose	10 mg q.d.
mode of administration	Oral (p.o)
Comparator product(s)	Not applicable
dose	Not applicable

mode of administration	Not applicable
Duration of treatment	1 year
Statistical methods	Descriptive analyses using summary statistics is planned for the primary endpoint of TEAEs and the secondary endpoints of change from baseline in haemoglobin and in CGI-S to EOT

FLOW CHART

Trial Periods	**Treatment**																**Follow-up**	
Visit	**1**[8]	**2**[8]	**3**[8]	**4**[8]	**5**[8]	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOT**	**eEOT**[9]	**FU1**	**FU2**
Weeks	**0**	**4**	**8**	**12**	**16**	**21**	**26**	**29**	**32**	**35**	**38**	**41**	**44**	**48**	**52**	**N/A**	**54**	**56**
Treatment day	**1**	**28**	**56**	**84**	**112**	**147**	**182**	**203**	**224**	**245**	**266**	**287**	**308**	**336**	**365**	**N/A**	**EOT/ eEOT +14**	**EOT/ eEOT + 28**
Visit time window (days)	N/A	±7	±7	±7	**±7**	**±7**	**±7**	±7	**±7**	±7	±7	±7	**±7**	**±7**	±7		±7	±7
Clinic (on-site) Visit[2]	X	X	X	X	X	**X**	**X**	☎	X	☎	X	☎	X	☎	X	X	X	X
Informed consent	X																	
Inform consent for biobanking[14]							X											
Demographics	X																	
Medical history	X																	
Physical examination							X								X	X		(X)
Weight	X[1]						X								X	X		(X)
Vital signs	X[1]	X	X	X	X	X	X		X		X		X		X	X	(X)	(X)
12-lead ECG				X			X				X				X	X		(X)
Drug screen test (urine)[3]	X[1]			X			X				X				X	X		
Pregnancy test[4]	X[1]	X	X	X	X	X	X		X		X		X		X	X		X
Safety Laboratory tests[3] Visit 3 and 5 Hematology panel only		X	X[H]	X	X[H]		X		X		X		X		X	X		X
PK Sampling[12]				X			X				X				X	X		
Biobanking[10]							X								X	X		
In-/exclusion criteria	X																	
Contact IRT	X	X	X	X	X	X	X		X		X		X		X	X		
(re)Dispense & administer trial drug at site	X	X	X	X	X	X	X		X		X		X					
IMP Compliance check		X	X	X	X	X	X		X		X		X		X	X		
Termination of trial drug															X	X		
[redacted]																		
[redacted]						[redacted]												
									X						X	X		
CGI-S						X									X	X		
[redacted]	[redacted]																	
													X					
Adverse events[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
[redacted]	[redacted]																	
Socioeconomic status																		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Substance use [6]							X								X	X		
C-SSRS[7]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAS/AIMS/BARS							X								X			
[redacted]	[redacted]																	
Exit interviews (patient and study partner)															X[13] →			
Inform consent for exit interviews															X →			

Trial Periods	**Treatment**																**Follow-up**	
Visit	**1[8]**	**2[8]**	**3[8]**	**4[8]**	**5[8]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOT**	**eEOT[9]**	**FU1**	**FU2**
Weeks	**0**	**4**	**8**	**12**	**16**	**21**	**26**	**29**	**32**	**35**	**38**	**41**	**44**	**48**	**52**	**N/A**	**54**	**56**
Treatment day	**1**	**28**	**56**	**84**	**112**	**147**	**182**	**203**	**224**	**245**	**266**	**287**	**308**	**336**	**365**	**N/A**	**EOT/ eEOT +14**	**EOT/ eEOT + 28**
Visit time window (days)	N/A	±7	±7	±7	**±7**	**±7**	**±7**	±7	**±7**	±7	±7	±7	**±7**	**±7**	±7		±7	±7
Clinic (on-site) Visit[2]	X	X	X	X	X	**X**	**X**	☎	X	☎	X	☎	X	☎	X	X	X	X
Patient Participation Completion																		X

X[H] Hematology panel only.

(X) Optional assessments at the discretion of the investigator

[1] If the procedure is performed at the last study visit for the parent trial, the procedure does not need to be repeated if visit 1 for trial 1346-0014 occurs on the same day, including split visit.

[2]Visits denoted as 'clinic' visits are to be performed on-site. Other visits may be conducted by telephone or on-site at the discretion of the investigator. Visits may be re-scheduled if the patient is experiencing an acute episode of psychosis (relapse). [redacted]

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

[4] Pregnancy test 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] After the individual patient's end of the trial, the investigator should report only any new occurrence of 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.

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

[7] C-SSRS may be performed more frequently based on investigator judgment or local regulation.

[8]Site staff should contact patients by phone approximately 2 weeks after the clinic visit to discuss adherence with study medication.

[9] Patients who permanently discontinue trial treatment should undergo the early End of Treatment (eEOT) visit as soon as possible, ideally within 7 days of IMP discontinuation, then complete the safety follow-up period.

[10] Collection of biobanking samples is optional. Serum/plasma samples will be collected at Visit 7 and EOT/Early EOT. Participants are required to sign a separate informed consent for biobanking. Samples will be stored at a biobanking facility for future research [redacted]

[12] 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 (preferably approximately 24 hours post last dose). For further details please refer to Appendix 10.1.

[13] Exit interviews are optional, and will be done at any time between EOT/eEOT and FU2 (in approved countries only).

[14] Biobanking consent can be collected at any visit prior to the collection of the sample at Visit 7.

TABLE OF CONTENTS

ABBREVIATIONS

AD	Alzheimer's disease
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIMS	Abnormal involuntary movement scale
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Products
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BARS	Barnes Akathisia Rating Scale
BI	Boehringer Ingelheim
BP	Blood Pressure
CA	Competent Authority
CGI-S	Clinical Global Impressions - Severity
CIAS	Cognitive Impairment Associated with Schizophrenia
C_{max}	Maximum Concentration
CNS	Central Nervous System
COVID-19	Corona Virus Disease-19
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organisation
CTP	Clinical Trial Protocol
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicidality Severity Rating Scale
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
dL	decilitre
DMC	Data Monitoring Committee
DSM – 5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

eDC	Electronic Data Capture
eEOT	Early End of Treatment
EOT	End of Treatment
[redacted]	
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GLYT 1	Glycine transporter 1
HAP	Human Abuse Potential
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
[redacted]	
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LPLT	Last Patient Last Treatment
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
NOAEL	No-observed adverse-effect level
NTI	Narrow therapeutic index
[redacted]	
PK	Pharmacokinetics
PI	Principal Investigator
PR	Pulse Rate

[redacted]

PoCC	Proof of Clinical Concept
q.d.	quaque die (once a day)
RDW	Red cell distribution width
REP	Residual Effect Period
SAE	Serious Adverse Event

[redacted]

SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal

[redacted]

WOCBP	Woman of childbearing 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, no cure and long-term impairments in day-to-day, social and occupational functioning associated with the disease [R10-5101, R20-1429] 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 facilities 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).

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 patient 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 CIAS and Iclepertin has the chance to be first to market 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.

Mode of action
Iclepertin is a potent and selective inhibitor of the 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. It is therefore expected that treatment with Iclepertin has the potential to improve cognition that was impaired by the schizophrenia illness.

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.

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 CYP3A and clinical drug-drug interactions studied were conducted

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 NOAEL with multiple exposures at 10 mg in humans 6-7x below the NOAEL.

Clinical Pharmacology
Iclepertin has a half-life ranging from 37 to 59 hr. Steady state is reached after 6 days of dosing with accumulation ratios for Cmax 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 Cmax 142% and for AUC0-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), we require morning dosing. Pharmacokinetic (PK) parameters between young and elderly healthy subjects, and between Japanese, Chinese and Caucasian subjects are comparable[c03572014, c03760676, c03724403].

Iclepertin crosses blood-brain barrier and the required 50% glycine increase in the CSF was observed after multiple dosing of 10 mg Iclepertin [c03724403]. .

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 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 Investigator site file (ISF), although the impact on common comedication in this target population is minimal. Details can be found in the Investigator Brochure that is updated and provided to sites at regular intervals[c02155957].

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 (AD) have been treated with Iclepertin for 12 weeks. The most frequent Adverse Events (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 AD, like trials with other GlyT1 inhibitors such as bitopertin [R15-1266, R18-1054], detected 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 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 Phase II trial 1346-0023 in patients with mild to moderate AD, results showed no evidence for efficacy of Iclepertin compared with placebo for the evaluated endpoints.

Summary
In summary, the non-clinical and clinical Iclepertin data demonstrated an acceptable profile to support clinical trials in males and females, 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 GLYT1) inhibitor. Inhibition of GLYT1 increases the concentration of the NMDA receptor co-activator glycine in the synaptic cleft thus modulating the effect of 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 with 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. PoCC was demonstrated for the primary endpoint of change from baseline in MCCB overall composite T-score after 12-week treatment [c31477880]. The adjusted mean change from baseline at Week 12 in MCCB overall composite T-score was nominally significant for the 10 mg and 25 mg treatment groups compared with placebo.

The Iclepertin phase III program is comprised of 3 pivotal trials that will investigate the efficacy and safety of Iclepertin in patients with schizophrenia over 26 weeks of treatment. Trial 1346-0014 is a roll-over trial that will offer patients who have completed 26 weeks of treatment with Iclepertin or placebo in any of the Iclepertin Phase III trials (1346-0011, 1346-0012 and 1346-0013) an opportunity to either continue or start to receive treatment with Iclepertin. Long-term safety data up to 1 year will be collected in this trial.

To address future scientific questions, participants will be asked in this trial to voluntarily donate biospecimens for banking (please see section 5.5). If the participant agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify participants that are more likely to benefit from a treatment or less likely to experience an AE, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

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 safe and well tolerated.

In addition, all entered subjects will continue on maintenance treatment with antipsychotic and other psychotropic medications. Background medication may be adjusted or changed by the investigator as deemed 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 score in the target population with schizophrenia.

So far, acquired clinical data suggest that Iclepertin improves cognition and this improved cognition is expected to lead to functional improvement in day-to-day activities. Patients with functional impairment related to schizophrenia 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, may benefit from treatment with Iclepertin.

Given the acceptable safety profile in clinical, nonclinical and toxicology studies performed to date, and careful monitoring planned during the study visits, the sponsor feels the risks to the participating patients are minimized and balanced by a potential benefit due to the intensive medical care received. Additional justification is the possibility to develop the first treatment options to improve cognition in patients with schizophrenia, which remains a high unmet medical need.

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 [c31477880]. 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 (IMP)		
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 [c02155957]for more details	Management of symptoms, evaluation, and follow-up as needed to ensure subject safety, per investigators clinical judgment.
Decrease in Haemoglobin	• 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. • PhII 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)]. On individual level we observed large overlap in Hb values between placebo and patients on Iclepertin.	• Patients who have had 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 in parent trial (assessed by the central lab) will be excluded from participation in this study. • Patients will be withdrawn from study treatment if more than 1 time drop in “haemoglobin level below 100 g/L (10g/dL) OR Hb decreases by 25% or more from baseline and is below the lower limit of normal”. • Please refer to section 5.2.6.2.5- ‘Hb 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 regard to the analysed ocular safety variables.	• Ocular AE will be monitored and followed up per investigators judgment (refer to section 5.2.6.2.4) • 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 be collected • Information from the ophthalmology examination will be collected in the Electronic Case Report Form (eCRF).
No long term use of Iclepertin	• Patients have been treated with Iclepertin for up to 12 weeks. Effects of long term use of Iclepertin is not known. The preclinical studies support clinical trials of chronic long-term administration in adults, including WoCBP.	In trials conducted to date, Iclepertin has been well tolerated by patients and there is no evidence that the tolerability is expected to change with long term use. The protocol is designed with frequent contact with patients and all AEs will be collected in the trial.

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**
Iclepertin- Drug Interactions		
Moderate or Strong CYP3A4 inhibitors	Exposure of Iclepertin will increase in presence of a strong and moderate inhibitor.	Patients should not be entered if taking any of the drugs listed in the ISF or need such drug during treatment period (refer section 3.3.3 and 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	
Trial procedures		
General discomfort blood draw	The potential risks of a blood draw include fainting and pain, bruising, swelling, or rarely infection where the needle is inserted. In rare cases a nerve may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch and persistent pain.	Management of discomfort, evaluation and follow-up as needed to ensure patient safety.
Disease Related Risk		
Worsening of Schizophrenia or relapse	Clinically stable patients with schizophrenia are entered 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 treatment to control symptoms. Definition of relapse provided to monitor in a standardized manner.

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		
Potential exacerbation of existing or new side effects caused by treatment with antipsychotics (e.g. tardive dyskinesia, orthostatic hypotension)	No worsening of schizophrenia or the AEs of antipsychotics were seen in phase II study	All AE will be collected throughout the trial. 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 ideations are common in this population. However, patients are in psychiatric treatment where continuous assessment of suicidal behavior and risk is well established. 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.
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.

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]: • 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%
Drug-induced liver injury (DILI)	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.
Human abuse potential (HAP)	According to the 2017 FDA guidance on "Assessment of Abuse Potential of Drugs", assessment of HAP is required for drug products "that contain CNS-active new molecular entities (NMEs)". Based on nonclinical data and completed Phase I studies and assessment of data from one completed Phase II trial in CIAS with Iclepertin, no signal of HAP has been observed, however human abuse liability of Iclepertin has not been formally investigated	A list of AE for assessment of potential abuse liability of Iclepertin will be provided as part of ISF and relevant AEs must be reported including verbatim description Investigators will be trained about the importance to assess patients for abuse and withdrawal related AEs Detailed information will be collected and monitored for study medication compliance >100% This monitoring strategy is consistent throughout the program

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 (COVID-19)	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 (minimizing time at the clinic, replace physical visits with remote visits, minimizing the use of public transportation to the site etc.). The investigators will take the totality of information related to each 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. The investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the patient.Considering the risk, patients with ongoing severe or serious SARS-CoV-2 infection at visit 1 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.During the treatment period if patient experiences severe or serious symptomatic infection with SARS-CoV-2, study medication will be temporarily stopped. If the study medication can't be restarted within 8 weeks, patient should be permanently discontinued from the study.

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		
Patient retention risk	Given the patient population and the long treatment period there is a risk of premature treatment discontinuation/patient withdrawal.	All patients in this study will be on active treatment. 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.
Risks of stopping study drug	In the Phase II study, following end-of-treatment, no increases in AEs were observed in patients treated with Iclepertin in comparison to those treated with placebo. Potential AEs after stopping study drug have not been formally investigated thus far and therefore cannot be fully excluded.	• Monitoring AEs for assessment of potential abuse liability are described above. • In one of the Phase III (parent) study(1346- 0012), 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 AEs of withdrawal from Iclepertin treatment Patients who stop therapy will undergo a 28 day off-drug follow-up period which will comprise of 2 visits with the site. During these visits, the patient will be assessed. It is expected that all AEs are followed until resolution or stabilization, in the opinion of the investigator.

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 safety assessment. The tasks and responsibilities of the DMC members will be detailed in the DMC charter.

1.4.3 Discussion

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 did not demonstrate relevant efficacy in the treatment of cognitive deficits of schizophrenia. Currently, there are no pharmacological treatments for CIAS approved by any regulatory agencies across the world. Pharmacological treatment of CIAS that would be available to all patients 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 objective of this trial is to collect additional safety data in patients with cognitive impairment due to schizophrenia, who participated in and completed the 26-week treatment period with Iclepertin or matching placebo of one of the phase III clinical trial program for Iclepertin (trial # 1346-0011, 1346-0012, 1346-0013).

2.1.2 Primary endpoint(s)

The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) throughout the extension study.

Note: TEAEs are defined as all AEs occurring between start of treatment in the extension trial and the end of its REP. AEs that start before first drug intake in the extension trial and deteriorate under treatment during the extension trial will also be considered as 'treatment-emergent'.

2.1.3 Secondary endpoint(s)

The secondary endpoints are:
- Change from baseline in Clinical Global Impressions – Severity (CGI-S) to end of treatment (EOT)
- Change from baseline in Hb to EOT.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multi-center, multi-national, open label, single arm extension trial in patients with cognitive impairment due to schizophrenia who have completed 26 weeks of treatment with 10 mg Iclepertin or matching placebo, taken once daily in one of the three phase III parent trials (trial 1346-0011, 1346-0012 or 1346-0013). Patients may be enrolled in this trial once the patient has signed the informed consent form and determined to have met all entry criteria for protocol 1346-0014.

Patients previously on active treatment in parent trial will continue to receive Iclepertin treatment and patients who were randomized to placebo in the parent trial will start receiving Iclepertin for the first time at Visit 1. Patients will receive treatment for 1 year.

After completion of the open label treatment, patients will have a 4-week safety follow-up. In addition to the collection of AEs, patients will be required to complete a number of assessments to monitor for symptoms and patient reported outcomes.

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

The main objective of this trial is to collect long term safety data in patients with CIAS. The primary endpoint therefore is the occurrence of TEAEs throughout the extension study.

An active control group is not planned in this extension study because there is no approved treatment for CIAS. Patients will be maintained on their background therapy, which may be adjusted according to investigator clinical discretion. This trial will provide an opportunity for patients who had received placebo in the parent trial to receive the active treatment.

It is acknowledged that the data for this open-label, single-arm trial will likely be biased due to, among others, selection and reporting bias. However, considering lifelong nature and potentially devastating consequences of cognitive impairment associated with schizophrenia, this trial will offer an active treatment to all patients who completed any of the randomized phase III trial 1346-0011 or 1346-0012 or 1346-0013. The decision to enter this trial will be made by the patient following a discussion with the investigator.

The aim of the study is to allow treatment continuation to individual patients; therefore, randomization, blinding and use of placebo would not be appropriate.

3.3 SELECTION OF TRIAL POPULATION

It is anticipated that approximately 1400 patients from approximately 240 sites, will complete one of the CONNEX studies (1346-0011, 1346-0012 and 1346-0013) and will consent to participate in this single arm extension trial where all patients will receive treatment with Iclepertin for 1 year.

Patients previously on active drug treatment will continue treatmet with Iclepertin, patients who received placebo will initiate treatment with Iclepertin for the first time at Visit 1 of the extension trial.

Re-screening of patients is not allowed.

3.3.1 Main diagnosis for trial entry

Clinically stable outpatients who have been diagnosed with schizophrenia (as per Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)) and have participated and completed one of the phase III trials with Iclepertin.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

In case of questions related to inclusion/ exclusion criteria's, please contact sponsor.

3.3.2 Inclusion criteria

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

2. Clinically stable outpatients who have been diagnosed with schizophrenia (as per DSM-5).

3. Patients, who completed 26 weeks of treatment in the parent trial, must enter the extension trial within[2]:
   - Within 2 weeks the EOT visit in 1346-0011, 1346-0013. (i.e. Follow Up 1 timepoint including the applicable time windows).
   - At the end of safety follow up in 1346-0012 (within the 7 days of visit Follow Up 6)

4. Women of childbearning potential (WOCBP)[1] 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.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
[2] Patients who had a temporary treatment discontinuation during the parent trial, but who restarted treatment and completed the planned EOT on study drug can be considered per investigator judgement

5. Have a study partner, defined as any person capable of understanding trial related procedures, with a minimum of 8th grade level of education, who knows the patient well, has been capable of interacting with the patient on regular basis (at least once a week, either private or professional). Study partner does not need to attend visits with the patient but must be reachable by phone. Study partner should preferably be the same person throughout the study, if possible
   - Professional study partner (e.g. study nurse, social worker etc.) are allowed if not involved in administering any of the protocol assessments.

3.3.3 Exclusion criteria

1. Participant who developed DSM5 diagnosis other than Schizophrenia or any condition that would prevent the patient from participating in the extension trial (e.g. stroke, head trauma, developed dementia, severe uncontrolled movement disorders or other significant condition since enrolment into the parent phase III trial (1346-0011, 1346-0012 or 1346-0013)).

2. Any suicidal behavior and/ or suicidal ideation of type 5 based on the C-SSRS in parent trial and up to and including Visit 1 of this study.
   - Patients with Suicidal Ideation type 4 in the C-SSRS (active suicidal thought with intent but without specific plan), in the past 3 months prior to and including Visit 1, can be entered in the study, if assessed and documented by a licensed mental health professional that there is no immediate risk of suicide.

3. Patients diagnosed with moderate or severe substance use disorder (other than caffeine and nicotine), as defined in DSM-5 while the patient was in parent trial and prior to Visit 1 of this study.

4. Positive urine drug screen ≥ 3 times during the parent trial based on central lab test.

5. Patients who are currently or wish to participate in another investigational drug trial.

6. Any clinically significant finding in the judgment of the investigator such as :
   - Clinically significant finding on he Physical examination and/or ECG from the last assessment done in the parent trial.
   - Vital signs (including blood pressure (BP) and pulse rate (PR)) 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.

7. Any significant central lab findings based on the last available lab result received during the parent trial such as:

- Severe renal impairment defined as an eGFR < 30mL/min/1.73m²,
- Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 times upper limit or normal or
- Hb drop below 100g/L (10g/dL) OR Hb decrease of 25% or more from baseline and is below lower limit of normal in parent trial (alert 3 from last measure Hb in parental trial)
- Patients who meet any of the withdrawal criteria before planned EOT (26 weeks) in parent trial.

8. Patients who have been diagnosed with hemoglobinopathies during the parent trial.

9. Patients with known ongoing severe or serious infection with SARS-CoV-2.

10. Known history of Human Immunodeficiency Virus (HIV) and/or known on-going Hepatitis B or C infections. As well as 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.

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

12. Patients with an allergy to Iclepertin and/or any of the excipients (including serious lactose intolerance). A list of Iclepertin and placebo ingredients are provided in the Investigator's Brochure.

13. Patients who are currently treated or expected to be treated with any of the following: strong or moderate CYP3A4 inhibitors, strong or moderate CYP3A4 inducers, CYP3A4 sensitive substrates,including grapefruit juice ad St. John's wort (Hypericum perforatum) and substrates with a narrow therapeutic range (e.g., fentanyl, cyclosporine).

3.3.4 Withdrawal of patients from treatment or assessments

Measures to control the withdrawal rate include appropriate explanation of the trial requirements and procedures prior to roll over from parent trial, as well as the explanation of the consequences of withdrawal.

Every effort should be made to keep the patients in the trial and on treatment unless there is a medical reason to discontinue treatment or patient fully withdraws consent for further study participation.

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 to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for AE collection reporting (please see sections 5.2.6.1 and 5.2.6.2).

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

3.3.5 Discontinuation of trial treatment

Temporary trial treatment discontinuation up to 8 weeks is allowed for medical or other reasons such as

- Resolution of Hb related issues
- Planned surgery
- SARS-CoV-2 infection
- Current treatment with Paxlovid

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

Patients who permanently discontinue the trial treatment prior to 52 weeks of treatment should complete an early end of treatment visit (eEOT) and the safety follow-up visits as outlined in the flow chart. Patients should be encouraged to complete these assessments as clinic visits.
The reason for early discontinuation of trial treatment (e.g. AE, consent withdrawal for study treatment) must be recorded in the eCRF. After the completion of the follow-up visits, the patient's participation in the trial will be concluded.

In rare cases, if patient refuses or is unable to visit the site for safety follow up after early discontinuation of trial treatment, the 14 and 28 day safety follow up visit may can be done remotely (e.g. by telephone) to collect as much patient safety data as possible.

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- 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
- Haemoglobin:
  - If Hb level drops (below 100 g/L (10g/dL) **OR** Hb decreases by 25% or more from baseline and is below the lower limit of normal) and does not return to normal in 8 weeks.
  - More than 1 time drop in "haemoglobin level below 100 g/L (10g/dL) **OR** Hb decreases by 25% or more from baseline and is below the lower limit of normal".

- If patient experiences severe or serious symptomatic infection with SARS-CoV-2, study medication will need to be temporarily stopped for a maximum of up to 8 weeks. If the study medication cannot be restarted within 8 weeks, patient should be permanently discontinued from study treatment.
- 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 has repeatedly shown to be non-compliant with important trial procedures and requirements and, in the opinion of both the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

  Example: consider cases on an individual basis, that have had repeatedly positive drug screen at 4 consecutive visits, or patients who are < 60% compliant with taking the study medication over 2 consecutive clinic visits.
- The patient needs to take any restricted medication that may impact the patient's safety to continue treatment, per investigator's clinical judgment. 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 5.2.6.2.

If new efficacy/safety information becomes available, Boehringer Ingelheim (BI) 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.

3.3.5.1 Withdrawal of consent to trial participation

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

Withdrawal of consent to the trial participation means permanently stopping the study treatment, plus no further participation in study visits, or 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 options for continued follow up outside of the trial after trial discontinuation.

Given the patient's agreement, the patient will undergo the procedures for eEOT, FUP1 and FUP2 as outlined in the Flowchart.

3.3.5.2 Discontinuation of the trial by the sponsor

BI 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, please see section 3.3.5.
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 3.3.5.1.
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.
All patients will be assigned to Iclepertin 10 mg once daily for 52 weeks.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Test product 1

Substance:	Iclepertin
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg
Posology:	10 mg once daily QD
Mode of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

The dose of 10 mg of Iclepertin once daily was selected based on the following strategy:

1. Effective dose in improving cognition in PoCC/DF trial in patients with schizophrenia was 10 mg, as this dose separated best from placebo w.r.t. 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 small with decrease of 3.3 g/L in 10mg group and 4.5 g/L in 25mg. It is planned to monitor Hb.
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.

4.1.3 Method of assigning patients to treatment groups

All patients will receive treatment with Iclepertin. Interactive Response Technology (IRT) will be used to dispense medication kits and manage initial/ resupply ordering of medication kits. The study site will be required to complete the appropriate module within the IRT system.

The investigator will receive all necessary instructions to access the IRT system from the Sponsor or chosen provider. Detailed IRT transactions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT provider. All medication kits assignments will occur in an open label fashion.

4.1.4 Drug assignment and administration of doses for each patient

Dispensing of medication kits will begin at visit 1. Sufficient medication kits (plus backup) will be provided at each clinic 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 52 weeks.
The first dose of study medication will be taken at the end of Visit 1 under supervision of the investigator or delegated site staff, after all Visit 1 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 study medication at home on the day of the clinic visit as patients will be dosed at the site. Dosing should occur approximately 24 hours after the drug administration from the preceding day.
The last dose of study medication should be taken on the day before the EoT Visit.
A dose reduction of Iclepertin is not possible.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open label trial, all patients will be receiving same dose of Iclepertin.

4.1.5.2 Unblinding and breaking the code

Not applicable

4.1.6 Packaging, labelling, and re-supply

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

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA) (as provided in the list of contacts) must be contacted immediately.

4.1.8 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 (CTP) by the IRB / ethics committee (EC)
- 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 (CA),
- Availability of the curriculum vitae of the Principal Investigator (PI),
- Availability of a signed and dated CTP,
- Availability of the proof of a medical license for the PI,
- Availability of FDA Form 1572 (if applicable).

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

The investigator 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 IMP and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all IMPs 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 listed 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 performed at Visit 7, EOT or eEOT (if applicable):
  - Antihistamines with prominent sedative side effects
  - Anticholinergics
  - Benzodiazepines
  - Other sedative medication
  - Short-term opioids (for pain, cough or diarrhea)

- Antihistamines and Anticholinergics:
  - Patients taking anticholinergics and/ or 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 opioid dependence (e.g. methadone) is not allowed during the trial period.

Allowed are:
- Non-systemic use (topical, inhalation or nasal administration) of antihistaminics and anticholinergics is allowed.
- Short-term opioid therapy up to 4 weeks per time, for example with cough syrup or pain killer, is allowed (except fentanyl).
- Vaccination with COVID-19 Vaccines is permitted as per local public health recomendations

4.2.2.2 Restrictions on diet and life style

Nicotine and caffeine use if possible should remain stable during the treatment period.

Patients should not donate blood while they are participating in 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.

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

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

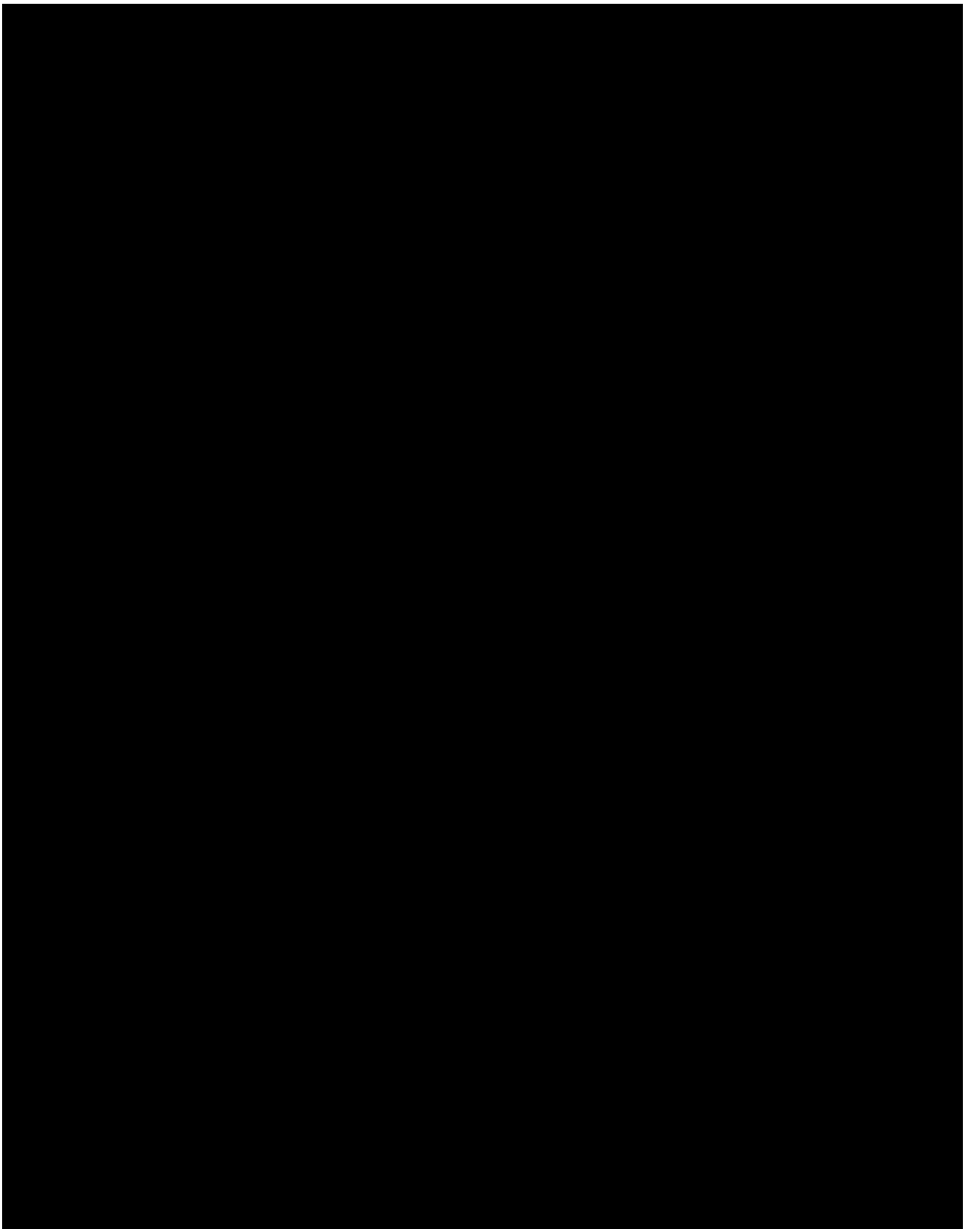
If the number of doses taken is not between 80-100%, site staff will explain to the patient the importance of treatment compliance and determine the reason (s) for deviation and document these in the source and eCRF

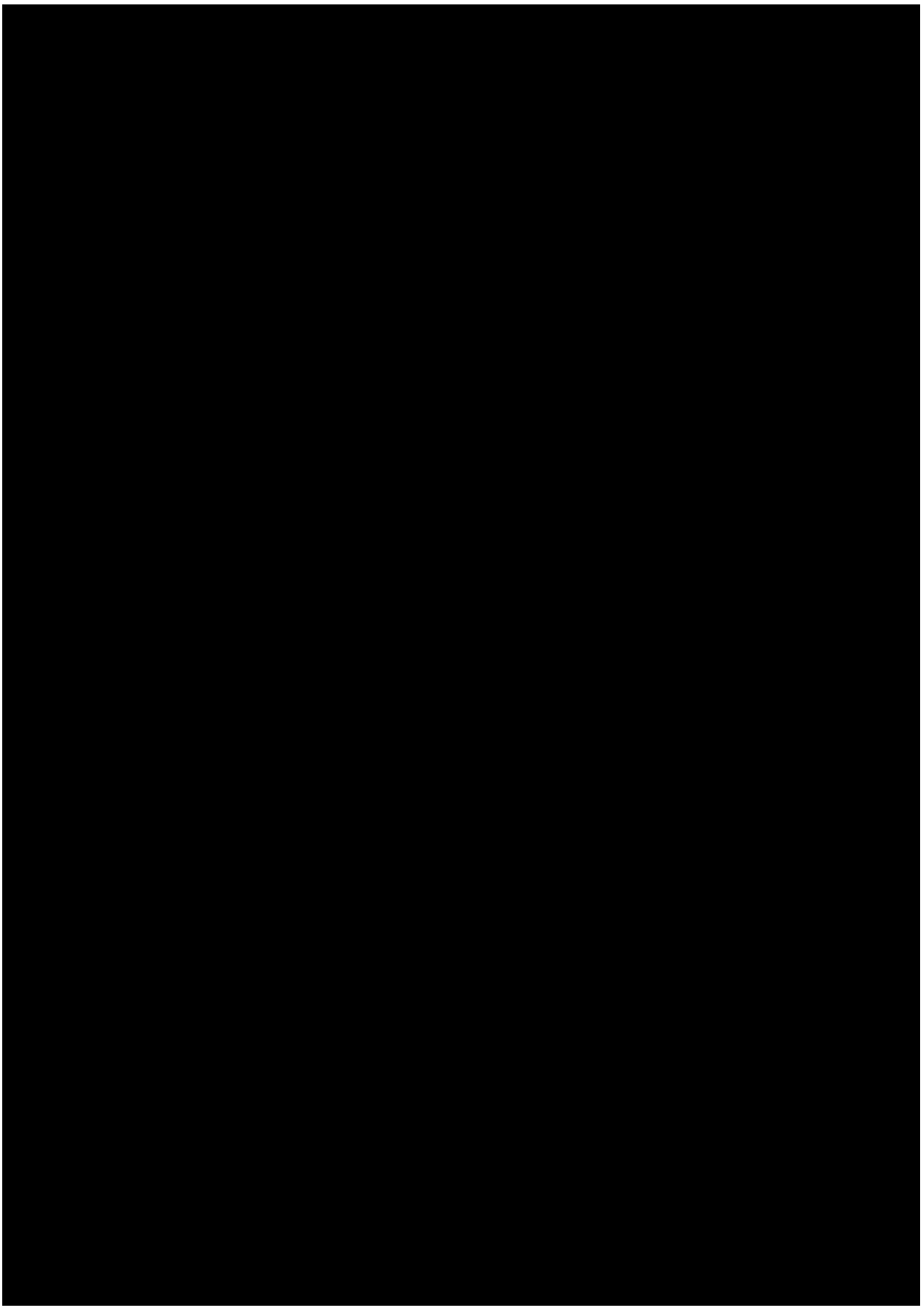
AEs related to HAP of Iclepertin should be reported and managed as per the investigator´s judgement.

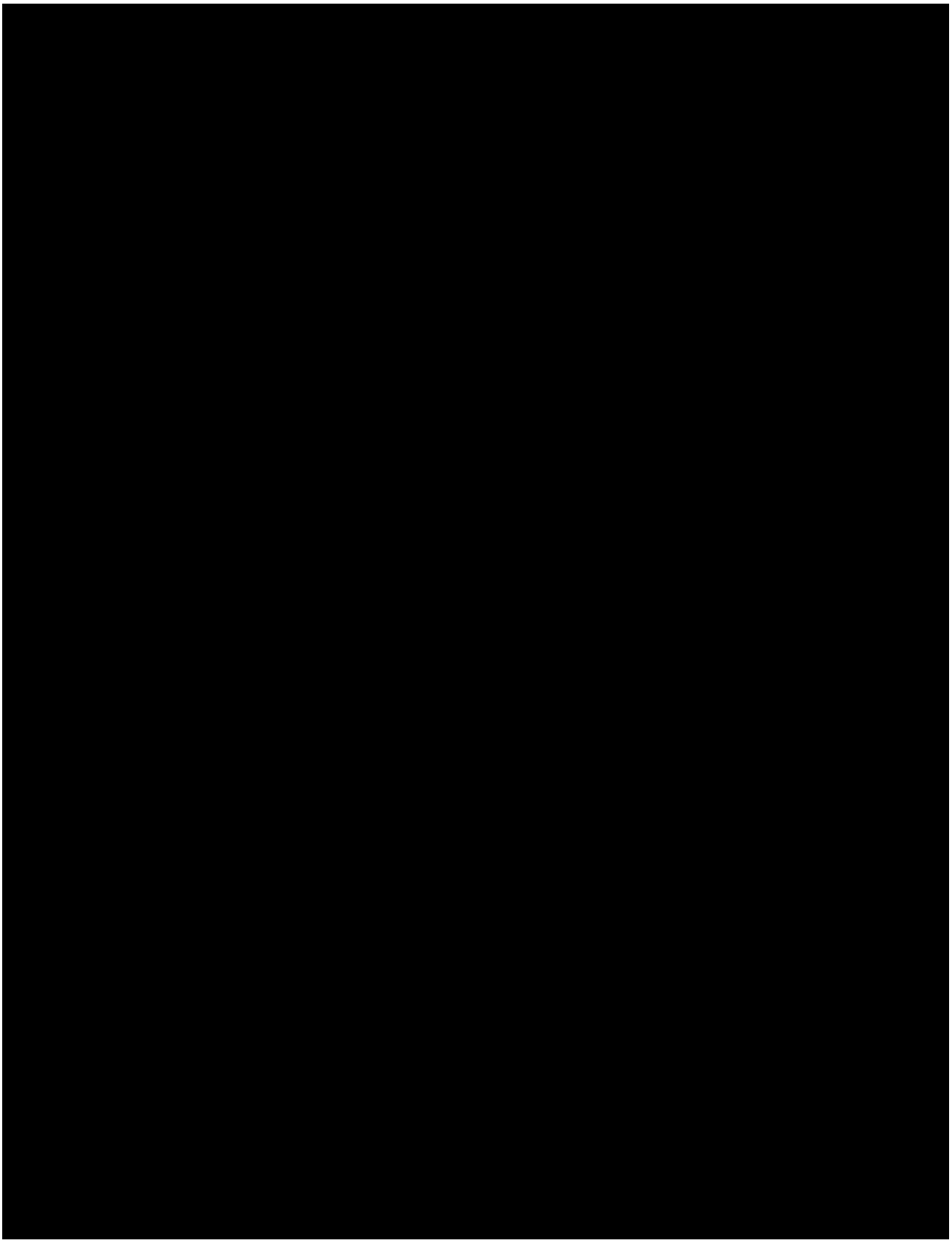
4.3.1 Medication adherence monitoring

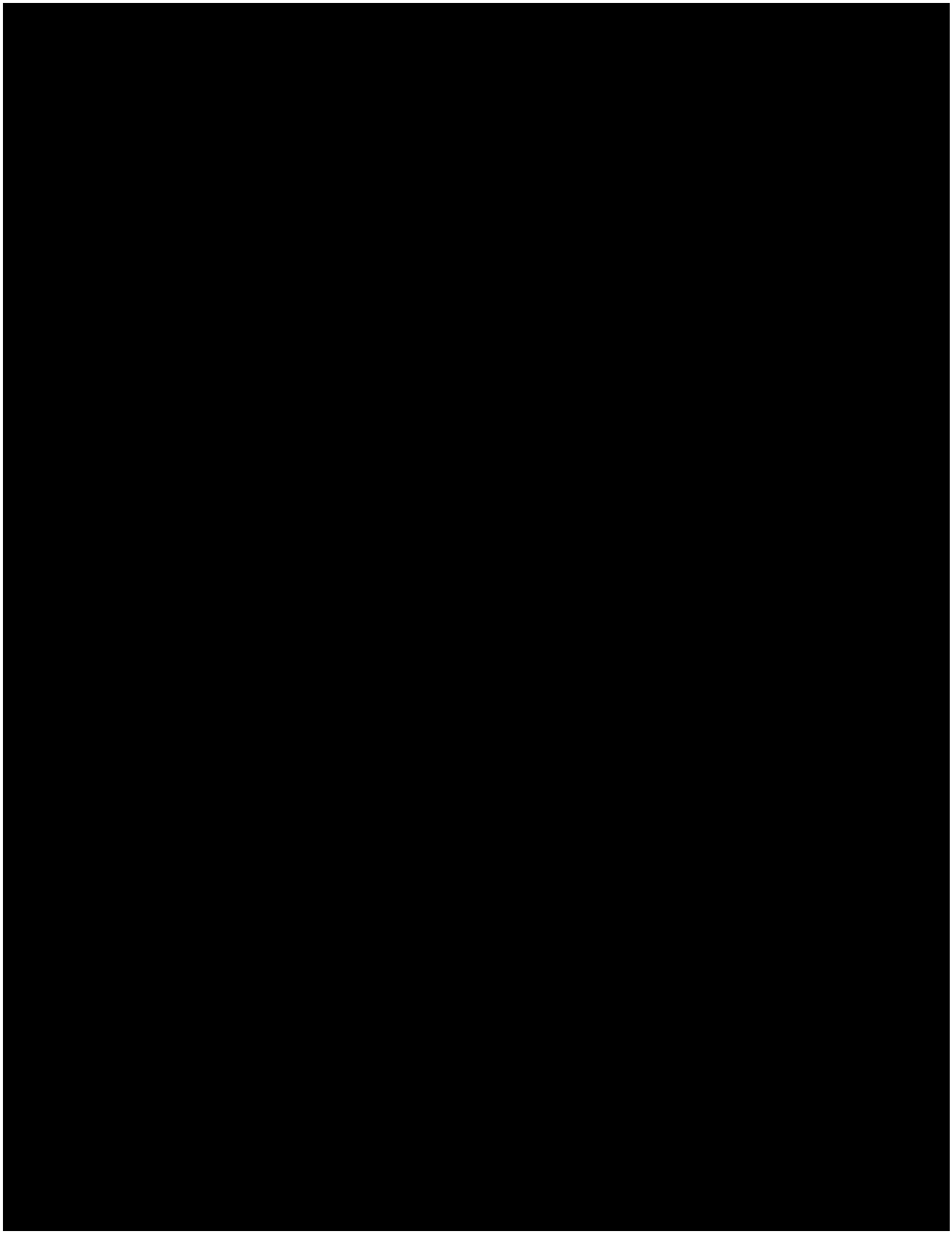
During the study, medication adherence monitoring may be introduced. In which case, in countries where it has been locally approved, the study medication will be packaged in smart blister cards fitted with a sensor to allow for electronic tracking (date, time, and cavity) when a medication is removed from the package. Each wallet with the smart blister cards contains medication for 28 days of treatment. Participants must be instructed to return all blister packs (empty, partially empty, or full) at each on-site study visit. Site personnel will dispense the smart blisters and read the returned smart blisters at each clinic visit to determine medication adherence. Inconsistencies in the electronically captured dispensing data should be discussed with the participant and the explanation documented.

5. ASSESSMENTS









[redacted]

5.2 ASSESSMENT OF SAFETY

- **Clinical Global impressions – Severity (CGI-S)** will measure the severity of the illness. The CGI-S is a one-item evaluation completed by the clinician on the patient's severity of psychopathology. The CGI-S is rated ordinal from 1 to 4 [R03-0520].

  Ideally, the same investigator or site staff should assess CGI-S (refer also to section 6.2.1 for additional information).

[redacted]

- **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), with a raw score of < 3 identifying "normal" symptoms, ≥ 6 indicating a level of disorder for which treatment should be reconsidered, ≥ 12 requiring attention, and a score of ≥ 18 "almost certainly" requiring modification of pharmacotherapy.

  - 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.

- **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 via a web-based portal. The results include the findings for suicidal ideation, intensity of ideation, suicidal behavior, and lethality / medical damage (for actual suicide attempts only).

FromVisit 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 flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Body weight will be measured at the time points specified in the flowchart.
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 flowchart, prior to blood sampling.

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

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 flowchart.

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

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

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

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as AEs (please refer to section 5.2.6).

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

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

Laboratory values that are out of range should be commented on lab report print-outs and evaluated by the investigator for clinical significance. Clinically relevant abnormal laboratory test results 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 CTP, at any time point during the study, per investigators discretion. Clinically significant abnormal laboratory results should also be reported by the investigators in the eCRF AE page (from subsequent visits test).

Table 5.2.3:1 Safety laboratory tests

Category	Test Name	
Haematology (refer to section 5.2.6.2.5)	Hb Hematocrit (Hct) MCV, MCH, RDW, MCHC Red Blood Cell Count/ Erythrocytes Reticulocyte Count Reticulocyte index Total iron binding capacity Serum ferritin Serum iron Platelet Count/ Thrombocytes	White Blood Cells/ Leukocytes Diff. Automatic (manual if diff. automatic is abnormal) - Neutrophils - Eosinophils - Basophils - Monocytes - Lymphocytes 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) Lactic Dehydrogenase (LDH) Lipase Amylase Cholesterol, total Triglycerides	Calcium Sodium Potassium Glucose HbA1c Urea (BUN) Creatinine Estimated Glomerular filtration rate (eGFR) * 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 Ketones Urobilinogen	Urine Bilirubin Urine blood Urine pH Urine Leukocyte esterase
Urine Drug Screen **** (Preliminary and confirmatory testing)	Amphetamines Barbiturates Cannabis Cocaine	Methadone Opiates PCP (Phencyclidine)

* 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.
**The following lab parameters will not be determined at each study visit:
TSH and Prolactin – only at EOT/ eEOT
*** To be done locally at site with central lab provided kit.
**** Patients will be considered drug screen positive, if the confirmatory test is positive.

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the flowchart. 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 abnormal findings noticed after baseline assessment will be reported as AEs and followed up and/or treated locally until normal or stable condition.

All ECGs will be transmitted electronically to the central ECG vendor in order to enable a centralized and independent re-evaluation of all 12-lead ECGs. A centralized and independent re-evaluation will be done. Central evaluation on individual ECG level will be performed by the vendor and a report will be provided to the site. Abnormalities detected during this centralized ECG evaluation will not necessarily qualify as AE. Decisions on eligibility for the trial and treatment or further follow-up of any findings are in the responsibility of the investigator. Abnormalities detected in central evaluation needs to be reviewed and if considered clinically significant to be reported as new AE, if identified after first dose in this extension trial. These Clinically relevant abnormal findings will be managed as medically appropriate, per investigators clinical judgment.

5.2.5 Other safety parameters

[redacted]. Refer to Section 5.2. In addition investigator may use CGI-S and [redacted] clinical judgment for assessing schizophrenia worsening/ relapse.

Schizophrenia worsening: 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 AE 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 AE. Definition of relapse for this program is: Increased level of care (such as hospitalization, home hospitalization, emergency room visit due to psychotic symptoms) due to worsening of psychotic symptoms increased [redacted] 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
- 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. However, if these abnormalities are AEs of the parent trial and still ongoing after first dose in extension trial, they should not be recorded as baseline conditions. In such situations section 5.2.6.2 should be followed.

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient 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: An event that possibly leads to disability will be handled as "deemed serious for any other reason" and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, BI 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 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 C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as SAEs by the investigator.

For each instance of suicidal ideation type 1, 2 or 3 after the start of the trial, the investigator is to decide based on clinical judgement whether this event represents an AE as defined in the protocol. If it is considered an AE then it must be reported as serious on the SAE form and eCRF AE page , as as "suicidal ideation" is included in the Always Serious AE 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 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:

Potential Severe DILI

A potential severe DILI that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other, or
- ALT, and / or AST elevations ≥10 fold ULN.

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

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 AE 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 (special notes on the SAE form reporting when needed):

For AEs with onset date in parent trial that are still ongoing after first dose of trial drug in extention trial:
- All ongoing AEs from the parent trial at the time of first dose of drug in this extension study, must be re-recorded and followed up in the extension trial.
- Updates for SAEs or AESIs from the parent trial that are ongoing after first drug dose in this extension trial must also be captured/updated in the concerned parent trial (1346-0011, 1346-0012 and 1346-0013) in addition to being recorded in this extension trial, as long as the database for the concerned parent trial is not locked. However, concerning reporting on the SAE form, the follow-up report will only be sent on the parent trial SAE form; no new SAE form is to be completed for the extension trial in such a situation.

Note:
If the intensity of an ongoing AE from parent trial changes after first trial drug administration in the extension trial, the AE with the new intensity will be handled as a new event; this means it is only recorded in the extension trial eCRF.
Example: If the intensity increased then the new AE name/term should contain “Worsening of…” or “Exacerbation of…”

Considerations for reporting on the SAE form, when intensity change qualifies as worsening/exacerbations of an event that had already been reported on the SAE form:
- corresponding follow up report to be sent on the parent trial SAE form with date of worsening as event end date.
- extension trial SAE form to be sent as initial report for the extension trial for new event “Worsening/Exacerbation of…” with date of worsening as onset date.

Considerations for reporting on the SAE form, when intensity change qualifies as worsening /exacerbation of an event and requires for the first time reporting on the SAE form (meeting for the first time seriousness/AESI criteria):

- only extension trial SAE form to be sent; as initial report for the extension trial for new event "worsening/exacerbation of…" with date of worsening as onset date.

For AEs with onset date after first dose of trial drug in extension trial:

Only to be reported in extension trial (concerning both eCRF and SAE form (when applicable)):

- From first dose of trial medication onwards until completion of 28 days follow up period (FU2) after the EOT visit: all AEs (non-serious and serious) and all AESIs.

- After the individual patient's end of the trial: the investigator does not need to actively monitor the patient for new AEs but should 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 contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and 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.

5.2.6.2.3 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.

5.2.6.2.4 Ocular AEs

Before drug administration at Visit 1 site staff will remind patients to report "any unusual visual perception they may experience"

During the study, if patients report a change in perception or any ocular adverse events, 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 AEs. 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.

5.2.6.2.5 Haemoglobin and anemia

Additional monitoring of patients who experience a decrease in Hb or anemia, as outlined below is required. In general patients should be monitored using the Haematology panel (refer to Table 5.2.3:1)

Any decrease in Hb should be managed as required per Investigators clinical judgement. Hb will be evaluated using the last on-treatment value from the parent trial in which values are blinded, therefore, site will be alerted if the following occurs:

Scenarios and Actions:
Alert 1:
- **Hb decrease > 20 g/L (2 g/dL) compared to baseline value**
  - Patients may continue on the study medication.
  - The hematology panel should be performed at the next visit (or earlier, per investigator's judgement). Hematology panel should be repeated at subsequent visits until resolution or stabilization or until subject completion.

Alert 2
- **Hb value is below the normal reference range**
  - Patients may continue on the study medication.
  - Haematology panel should be performed at the next visit (or earlier, per investigator's judgement). Haematology panel should be repeated at subsequent visits until resolution) or stabilization (alerts are no longer triggered) or until subject completion.

- 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.

Alert 3

- **Hb value < 100 g/L (10g/dL) OR**
  decrease of ≥25% from baseline and is below the lower limit of normal
  - Patients will need to **temporarily stop** the study medication.
  - Report as an AE "Anaemia"
  - Patient should be referred to a specialist for further management.*
  - Haematology panel should be performed at the next visit (or earlier, per investigator's judgement). Haematology panel should be repeated at subsequent visits until resolution or stabilization or until subject completion.
  - **After first drop:**
    - If Hb value does not return to normal within 8 weeks, patient should be permanently discontinued from study treatment and eEOT should be conducted.
    - If Hb values returns to normal within 8 weeks, study medication can be restarted per investigators clinical judgment.
  - **If Hb drops second time** *(Hb value <100 g/L (10g/dL) OR decrease of ≥25% from baseline and is below the lower limit of normal)* after restart of study medication, patient should be permanently discontinued from study treatment and eEOT should be conducted.

*Note - The specialist evaluation should be documented in the source. Any clinically relevant finding or diagnosis from this consultation should be considered while reporting AE(s).

5.2.6.2.6 AE suggestive of study medication abuse potential

To assess the abuse potential of Iclepertin, investigators are required to provide detailed descriptions of specific types of AEs and scenarios that are suggestive of study medication abuse (e.g. inappropriate medicating dosing). Detailed information should be recorded in the source documents and eCRF and if applicable, on the SAE form. A list of AEs potentially indicating study medication abuse will be provided as part of ISF.

5.2.6.2.7 Monitoring of potential adverse events after stopping the study medication

All patients will be closely monitored during the safety follow up period to assess potential AEs of withdrawal from Iclepertin treatment. In addition, patients will undergo assessments with [redacted] and C-SSRS.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

PK 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

A detailed description of sample collection and handling is provided in the laboratory manual. 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.

Plasma samples will be discarded at latest 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. The aim of the collection/banking is to be able to analyse long term and late effects of treatment, as well as to potentially evaluate the persistence effect on biomarkers in prolonged treatment. Biobanking will occur in countries where it has been locally approved and only after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Samples will be collected only in countries where all applicable local regulatory and ethics.
approvals have been obtained for biobanking.

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 plasma and serum banking purposes.

5.6 OTHER ASSESSMENTS

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.

Exit interview, in selected countries, and where it has been locally approved, trained independent moderators will interview approximately 40 patients and approximately 15 study partners at EOT or within a time window of approximately 4 weeks after. Participants will respond to open-ended questions on their experience in performing daily tasks and activities whilst taking Iclepertin including meaningfulness and importance of the changes they experienced in daily functioning. Participants will also respond to open-ended questions on their overall experience of treatment and participation in the clinical study. For participants who prematurely discontinue the study, the interview can be conducted after their eEOT. Participation in the interview is optional, details will be described in an optional inform consent form. Further details will be provided in a separate interview manual.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

The scheduled measurements are appropriate to see drug induced changes in physical examination, vital signs, ECG and standard laboratory values. These primary and secondary safety measurements are standard and accepted for evaluation of safety and tolerability of an oral drug, and they are widely used in this kind of studies. The period of 1 year of treatment with Iclepertin is deemed appropriate to collect additional safety data in patients with cognitive impairment due to schizophrenia

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 are to adhere to the visit schedule as specified in the Flow Chart including time windows for rescheduling. Preferably the visits should be conducted in the morning.

If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule calculated from Visit 1. 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

It is the responsibility of the PI 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 [redacted]C-SSRS [redacted] CGI-S, SAS, AIMS, BARS, [redacted] require vendor certification.

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 AE.

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

Safety labs, urine drug screen, pregnancy test, physical exam, vital signs assessment, C-SSRS may be performed more frequently based on investigator discretion or if required locally.

The following are preferences for the conduct of the assessments:

[redacted]

- All other assessments can be completed per the convenience of patient and site at all respective visits.

[redacted]

- Assessment of each rating scale [redacted]CGI-S) should preferentially be done by the same rater for a given patient throughout the study period. However, for [redacted] the consistency of time of day is more important than the consistency of the rater.
- The global impression anchor scales (CGI-S) should preferably be assessed after [redacted] at the respective visits when they are scheduled.

[redacted]

- During the [redacted] assessments and throughout the visit, patients are allowed to take short breaks as needed, in the judgement of the rater/investigator.
- 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.
- Study procedures for visits 6, 7, 9, 13, EOT and eEOT can be split into 2 sequential days in which case the following is preferred:
  - Each assessment should be completed on the same day.
  - [redacted] o be done on the first day of the visit
  - The remaining assessments can be done per convenience of the patient and site on day 1 or day 2
  - [redacted] are recommended to be done on the same day to reduce the burden to the study partner (applicable for V6, V13 and EOT/ eEOT) It is important that the patient and the study partner portions should be done same day or consecutive days as the interview refers to a specific timeframe.
  - CGI-S anchor scale to be done after [redacted] . The CGI-S rater should base their assessment after review of information about that patient at that visit, including the [redacted] ratings.
  - 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.

Other important considerations:
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.

Study partner requirements:
- Input from study partners will be required on the following assessments as indicated in the flow chart.

[redacted]

- If the study partner is not available for in person ratings, telephone interview is acceptable. The study partner must be available within visit window for a telephone interview at the visits indicated in the flowchart where study partner questionnaires are required.
- Preferably the study partner should remain constant throughout the trial period

For study partners who are also caregivers:

- Study partners who are also caregivers will be asked to complete the [redacted] (optional assessments) as indicated in the flowchart. 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 [redacted] this should be as close to the visit as possible, preferably within the study visit window.

6.2.2 Treatment period

- Treatment period is from Visit 1 to (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.
- Please refer to flow chart for procedures to be performed at each visit.

Visit 1:

- Signed informed consent must be obtained from the patient before performing any study related procedure.
- Study partner must sign informed consent form before performing any relevant study related procedure (V6).
- All procedures for parent trial last visit should be completed before first dose of this extension trial.
- Some procedures that have been performed at the last visit for the parent trial do not need to be repeated. Refer to Flow chart.
- The patient is recorded on the enrolment log and registered in the IRT system.
- Please refer to the general requirements in section 6.2.1
- **Drug of abuse testing**; At visit 1 the investigator should remind the patients of the importance of not taking drugs of abuse during the study and that urine testing will be repeated throughout the trial.
- **Medical history** will be collected from parent trial.
- **Baseline conditions:**
  - Any Baseline Conditions/ Medical History entries that are ongoing at the end of participation in the parent trial are to be re-recorded in the extension trial case report form (CRF)

- If concomitant medication is being taken for a Baseline Condition/ Medical History reported in the parent trial, re-record the Baseline Condition/ Medical History in the extension trial CRF.
- Any AE from the parent trial that is Resolved with 'sequelae' should be entered as a Baseline Conditions/ Medical History in the extension trial.
- For any newly identified Baseline Condition/Medical History in the extension trial:
  - Any newly identified baseline condition that has been identified and was relevant at the time of the subject participation in the parent trial and the parent trial is not locked- record this information in the parent trial and in the extension trial CRFs, as applicable.
  - Any newly identified baseline condition that has been identified and was relevant at the time of the subject participation in the parent trial and the parent trial is locked- record this information in the extension trial CRF.
  - Any newly identified baseline condition that has started after participation of the parent trial and is present at the start of the extension trial, record the extension trial only.

- **Concomitant Medications/Non-Drug Therapies**
  - Any Concomitant Therapy/Non-Drug Therapies that are ongoing at the end of participation in the parent trial are to be recorded in the extension trial CRF.
  - For newly identified Concomitant Therapy/Non- Drug Therapies in the extension trial:
    - Any newly identified Concomitant Therapy/Non- Drug Therapies that has been identified and was relevant at the time of the subject participation in the parent trial and the parent trial is not locked- record this information in the parent trial and in the extension trial CRFs, as applicable.
    - Any newly identified Concomitant Therapy/Non- Drug Therapies that has been identified and was relevant at the time of the subject participation in the parent trial and the parent trial is locked- record in the extension trial CRF.
    - Any newly identified Concomitant Therapy/Non- Drug Therapies that have started after participation of the parent trial and is occurring at the start of the treatment of the extension trial, record the extension trial only.
- **First intake of trial drug will be done at the site.**
- **Adherence monitoring:** at visit 1 patients should receive information on adherence monitoring system and it's packaging (if site is participating and if approved at the time of the visit).
- **Medication kits will be dispensed**

For treatment visits (including Visit 1 as applicable):

- 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 at each on site visit will be dispensed

- 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.

- **A phone call to discuss adherence to study medication should be done approximately 2 weeks after each visit from V1 to V5**.

- Pre dose PK 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.

- At Visit 14, patients will be instructed to take the last dose of study medication on the day before the EOT Visit.

Unscheduled visits

Unscheduled visits can be done at any time at the discretion of the investigator.

6.2.3 End of Treatment visit and Early end of treatment visit

Please refer to the flow chart for procedures to be completed.

The final [redacted] assessment at the EOT Visit should be performed after the patient completes the 52 week treatment period.

- Patients who permanently discontinue trial treatment early should undergo the eEOT visit, ideally within 7 days of IMP discontinuation, then complete the safety follow up period.

- Termination of trial medication eCRF pages will be completed.

- Exit interviews will be requested as an optional procedure for subjects and their study partners in selected countries, approximately 4 weeks after EOT. The interview will be conducted after a separate exit interview informed consent has been given in accordance with local ethical and regulatory requirements.

6.2.4 Follow-up period and trial completion

- Patients who complete 52 weeks of treatment or permanently discontinue medication early will be followed at FU1 and FU2. Refer to flow chart for procedures. The planned observation period is defined as 52 weeks of treatment.

- Patients who have been early discontinued from study treatment because of Hb related withdrawal criteria, should be monitored and followed up during the safety follow up with Haematology panel.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The objective of this trial is to collect additional safety data in patients with cognitive impairment due to schizophrenia, who have completed 26 weeks of treatment in one of the parent phase III clinical trial program for Iclepertin (trial # 1346-0011, 1346-0012, 1346-0013). No hypothesis testings will be performed. Analysis relating to the primary endpoint will be descriptive in nature.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The treated set (TS) will consist of all patients who enter this roll-over trial and receive at least one dose of open-label study medication. Treated set will be used in all of the analyses which will be descriptive in nature.

Unless otherwise specified, baseline will be defined as the last measurements (including measurements in the parent trial) before first drug intake in this extension trial. Additional details will be provided in the TSAP. For the secondary endpoint of Hb level, baseline will be defined as the last on-treatment value from the parent trial, i.e. the last available value collected at or before the end of treatment visit of the parent trial.

7.2.2 Primary endpoint analyses

All safety analyses will be performed on the treated set.

Primary endpoint analysis will be a descriptive anlaysis of the frequency of subjects with TEAEs.

Further analyses of AEs will be part of the planned safety analyses in Section 7.2.5.

7.2.3 Secondary endpoint analyses

For the secondary endpoints of Hb level and CGI-S, descriptive statistics assessing the change from baseline to EOT will be provided.

[redacted]

7.2.5 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP, a period of 12 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent adverse events, i.e. all AEs occurring between start of treatment and end of the REP. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

The frequency of subjects with (S)AEs will be summarised by primary system organ class (SOC) and preferred term (PT). The SOCs will be sorted by default alphabetically and PTs will be sorted by frequency within an SOC. Separate frequency tables will be provided for patients with different treatment emergent AEs.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised.

Vital signs, physical examinations, or other safety-relevant data observed at 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 analysis
Plasma concentrations of Iclepertin at related time points will be analysed descriptively as further explained in Appendix 10.1.

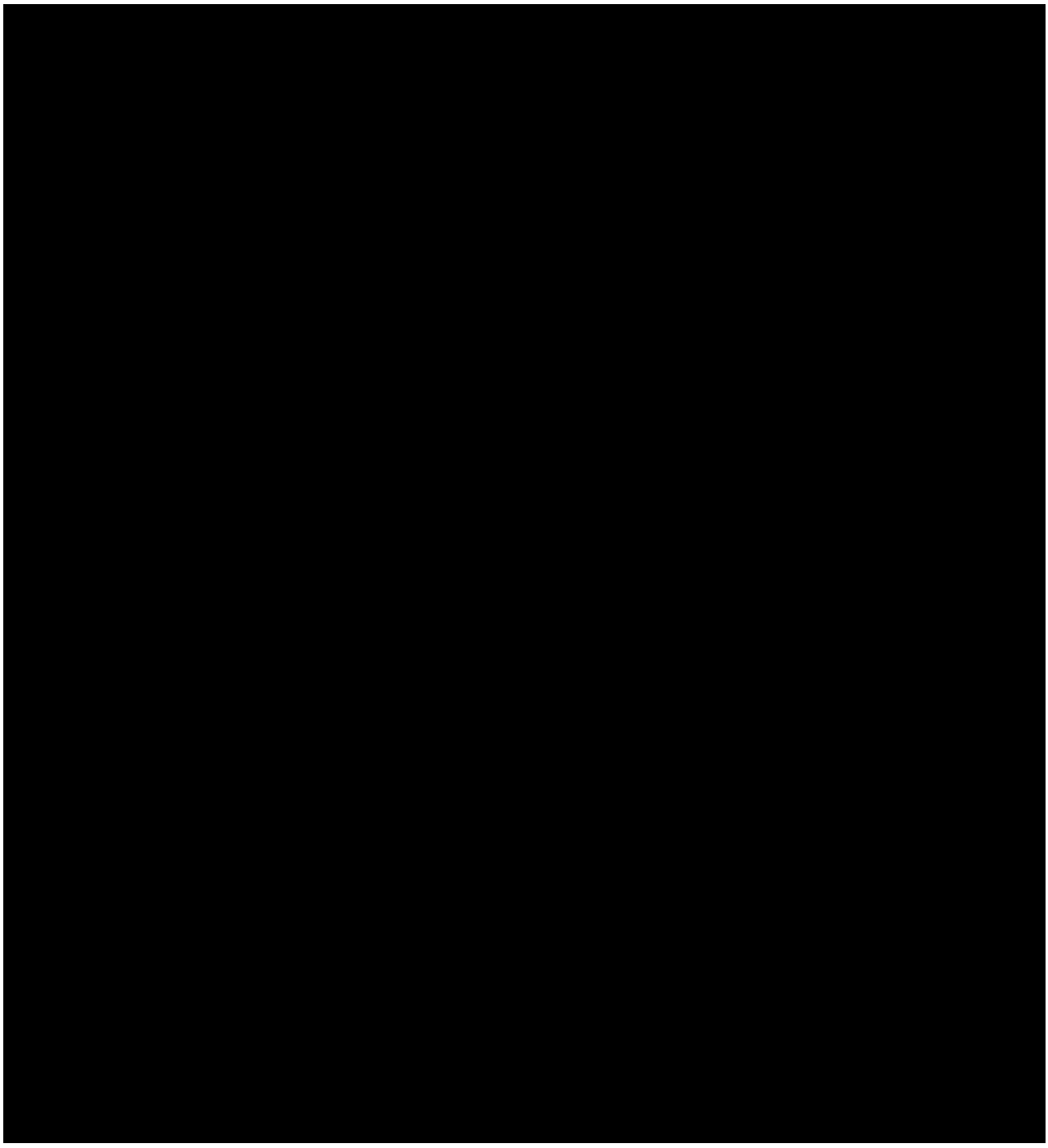
7.2.7 Interim Analyses

Interim analyses could be performed to support MAA/NDA submission and registration or upon request from Health Authorities. All of the above specified analyses may be presented at each interim analysis. No statistical adjustment due to multiple testing is required for these

interim analyses since no confirmatory hypothesis testings are planned for this trial. Interim analysis will include all available data collected up to the snapshot date. Safety will be monitored by an external and independent DMC.

7.3 HANDLING OF MISSING DATA

If not specified otherwise, missing data will not be imputed and will remain missing. Potential outliers will be reported and analysed as observed.



Any additional details on the handling of missing data will be specified in the TSAP.

7.4 RANDOMISATION

There will be no randomization for this extension trial. All subjects entered this trial will be treated open-label with the Iclepertin 10mg.

7.5 DETERMINATION OF SAMPLE SIZE

Not applicable as this is an extension trial. The total number of patients included in this trial will correspond to the number of patients who have completed one of the three parent phase III trials (1346-0011 or 1346-0012 or 1346-0013) and who did not prematurely discontinue trial medication, and fulfilled the eligibility in this trial and are willing to participate.

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

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH-GCP, relevant BI Standard Operating Procedures (SOPs 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 BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to 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 CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to their participation in the trial, written informed consent must be obtained from each, patient (or the patient’s legally accepted representative) and the patient’s study partner 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 based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

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

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. 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 the assigned vendor. 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
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (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 "**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 Suspected Unexpected Serious Adverse Reactions occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim.

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 (to the parent trial treatment assignments) 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 PIs (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, 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, 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 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 and an IRT vendor will be used in this trial. Details will be provided in the respective manuals, available in the ISF.

9. REFERENCES

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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 during treatment course 1

Visit	Day	Time Point [hh:min]	CRF Time/ PTM	Event	Sample No
4	84	Preferably within 30 min before drug administration	~0:30	Pre-dose PK Blood	1
7	182				2
11	266				3
EOT	365	~1 day after last dose	~24:00*	Post-dose PK	4
(e) EOT	-	~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 [redacted] for caregiver asses tudy partner IC
The study partner must interact with the patient on a regular basis at least once a week.	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.
[redacted]	

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

No patient should be entered in the study unless all Visit 1 procedures are completed in the clinic as per the standard CTP.

In case of any restrictions during the COVID-19 pandemic or any other exceptional cirmcumstances (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 needs 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) may be done as a home visit or telephone / video conference or locally (e.g. at a local lab, diagnostic centre, 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 have been introduced to ensure patient safety and appropriate trial continuation based on a thorough benefit-risk assessment of treatment continuation versus early discontinuation, to be judged by the investigator on an individual patient level whereby patient safety always needs to be at the centre of decision-making (see Section 1.4).

In exceptional circumstances, due to administrative delays to site becoming regulatory ready for the first patient visit, the enrolment may be approved by the sponsor after discussion.

The following study data should be collected/ reported during home and/or remote visit:
- Birth control check (for women of childbearing potential)
- Safety and pregnancy test
- Vital Signs
- ECG
- AEs
- Concomitant Therapies
- All scheduled scales and questionnaires (if possible)
- Study medication compliance check

Birth control check (for women of childbearing potential) during phone/ remote visit

- 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 flowchart or is required based on local regulations or investigators discretion.

Safety assessments

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

- 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 documentation.
- At a minimum the hematology 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 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 kit to their site staff, if needed and 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.

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.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		09 Mar 2023
EudraCT number **EU number**		2020-003745-11
BI Trial number		1346-0014
BI Investigational Medicinal Product(s)		Iclepertin
Title of protocol		An open label, single arm, extension trial to examine long-term safety of Iclepertin once daily in patients with schizophrenia who have completed previous Iclepertin Phase III trials.(CONNEX-X)
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		The International Nonproprietary Names for Pharmaceutical Substances listed Iclepertin for BI 425809.
Section to be changed		Protocol synopsis
Description of change		Number of countries change from 32 to 42
Rationale for change		Addition of countries in the parent trials
Section to be changed		Protocol synopsis
Description of change		Main in and exclusion criteria added Follow up 1 visit window for subjects entering the study from studies 1346-0011 and 1346-0013. Added for subjects entering the study from study 1346-0012 within 7 days of Follow Up 6
Rationale for change		To clarify, that subjects have the visit window of the last visit from parent trial to enter the study.
Section to be changed		Flow chart
Description of change		Added a separate line item for informed consent for biobanking, and footnote #14 to clarify biobanking can be collected anytime before Visit 7.
Rationale for change		Clarification of the required timepoint in which it should be performed
Section to be changed		Flow chart
Description of change		Addition of [redacted] at EOT, addition of CGI-S at visit 6, removing CGI-S from visit 4, 7 and 11

Rationale for change		To align the assessment of CGI-S with the timing of the SCoRS
Section to be changed		Flow chart
Description of change		Days of first treatment changed to treatment days
Rationale for change		To clarify day 1 is the first day of treatment
Section to be changed		Flow chart footnotes
Description of change		Footnote 13 was corrected to 12
Rationale for change		correction
Section to be changed		Flow chart, flowchart footnotes and section 5.6 Other Assessments
Description of change		Added Exit interviews and Informed consent for exit interview. Addition of footnote #13
Rationale for change		Implementation of optional patient and study partner interviews to collect feedback on their study experience.
Section to be changed		Abbreviations
Description of change		Addition of Abbreviations; HIV and [redacted]
Rationale for change		Correction
Section to be changed		Table 1.4.2:1 and section 5.2.6.2.4
Description of change		Change from Vision AEs nomenclature to Ocular AEs and change the requirement for ophthalmologic assessments must to be performed in case of moderate to severe intensity vision
Rationale for change		Request from FDA to have all ocular AEs assessed by an ophthalmologist.
Section to be changed		Table 1.4.2:1 and section 3.3.5
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		1.4.3
Description of change		Addition of reference R20-0592 listed in section 9.1
Rationale for change		Correction of administrative error
Section to be changed		[redacted]
Description of change		
Rationale for change to be changed		

Section to be changed		[redacted]
Description of change		
Rationale for change to be changed		
Section to be changed		Inclusion criteria
Description of change		Inclusion criteria #3, added Follow up1 visit window for subjects entering the study from studies 1346-0011 and 1346-0013. Added for subjects entering the study from study 1346-0012 within 7 days of Follow Up 6
Rationale for change		To clarify, that subjects have the visit window of the last visit from parent trial to enter the study.
Section to be changed		Section 3.3.3
Description of change		Exclusion # 1, added phase III trial numbers
Rationale for change		Clarification
Section to be changed		Section 3.3.3
Description of change		Exclusion Criteria #12 updated
Rationale for change		Clarification that list of ingredients can be found in the Investigator's Brochure
Section to be changed		Section 3.3.5
Description of change		Addition of new reason for withdrawing (patient 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 3.3.3.5.2
Description of change		Bullet correction in reasons for trial discontinuation by sponsor
Rationale for change		Clarification, correction of formatting error.
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 4.3
Description of change		Clarification on calculation of compliance based on empty table counts (number of tablets removed from package).

Rationale for change		Clarification
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		Correction
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change to be changed		Correction
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change to be changed		Clarification, they were previously described in section 2.2.2
Section to be changed		Section 5.2
Description of change		Correction on CGI-S rating 1-4
Rationale for change to be changed		Correction
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change to be changed		[redacted]
Section to be changed		Section 5.6
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		Section 5.6
Description of change		Addition of exit interview details
Rationale for change		To collect subject and study partner overall experience of treatment and participation in the clinical study including meaningfulness and importance of experienced changes.
Section to be changed		Section 6.2.1
Description of change		Addition of scales that require rater vendor certification
Rationale for change		Clarification
Section to be changed		Section 6.2.1
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		Section 6.2.1
Description of change		Clarification of preferences if visits are split into sequential days
Rationale for change		Clarification
Section to be changed		Section 6.2.1

Description of change		Clarification study partner must be available within study window
Rationale for change		Clarification
Section to be changed		Section 6.2.2
Description of change		Medical history removed the word pooled
Rationale for change		Clarification
Section to be changed		Section 6.2.2
Description of change		Added reference to appendix 10.3 for guidance on exceptional circumstances.
Rationale for change		Ensure sites are aware of potential adaptations in case of exceptional circumstances
Section to be changed		Sections 6.2.2 and 8.1
Description of change		Updated paragraph regarding patient and study partner informed consents
Rationale for change		Clarification that patient can start trial procedures if the study partner informed consent is not yet signed.
Section to be changed		Sections 6.2.2
Description of change		Clarification of timing when the subject receives information on the adherence monitoring system
Rationale for change		Clarification
Section to be changed		Sections 6.2.3
Description of change		Addition of exit interviews description and it's consent
Rationale for change		To describe the timing of the optional exit interviews and it's consent
Section to be changed		Sections 6.2.4
Description of change		Definition of the planned observation period
Rationale for change		To clarify the plan observation period comprehends the 52 weeks of treatment
Section to be changed		Section 7.2.1
Description of change		Added the following definition : For the secondary endpoint of Hb level, baseline will be defined as the last on-treatment value from the parent trial, i.e. the last available value collected at or before the end of treatment visit of the parent trial
Rationale for change		Clarification
Section to be changed		Section 9.1
Description of change		Addition of missiong reference R03-0520
Rationale for change		Correction
Section to be changed		Section 10.1
Description of change		Correction on visit 7 day deleted 187 and entered 182
Rationale for change		correction
Section to be changed		Section 10.2

Description of change		Study partner interaction with patient change from minimum listed to "on a regular basis at least once a week"
Rationale for change		To align with inclusion criteria #5
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		Addition; In exceptional circumstances, due to administrative delays to site becoming regulatory ready for the first patient visit, the enrolment may be approved by the sponsor.
Rationale for change		To allow case by case consideration of enrollment delay in exceptional circumstances
Section to be changed		Section 10.3
Description of change		Include analysis by the Central Lab in addition to blood sampling, removed erroneous reference to CRF
Rationale for change		Include description in case the Central Lab is in 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		[redacted]
Rationale for change		Clarification that those assessments cannot be performed remotely.

11.2 GLOBAL AMENDMENT 2

Date of amendment		18 Sep 2023
EudraCT number **EU number**		2020-003745-11

BI Trial number		1346-0014
BI Investigational Medicinal Product(s)		Iclepertin
Title of protocol		An open label, single arm, extension trial to examine long-term safety of Iclepertin once daily in patients with schizophrenia who have completed previous Iclepertin Phase III trials.(CONNEX-X)
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Flowchart
Description of change		Substance use added to the flowchart for eEOT
Rationale for change		To align with the CRF
Section to be changed		Flowchart footnote
Description of change		Added “including split visit” to footnote number 1. 1 If the procedure is performed at the last study visit for the parent trial, the procedure does not need to be repeated if visit 1 for trial 1346-0014 occurs on the same day, including split visit.
Rationale for change		Clarification
Rationale for change		DMC recommendation
Section to be changed		Table 1.4.2:1 Overview over trial related risks
Description of change		Sucidiality section updated to clarify in case of a positive report of suicidal behavior and/or suicidal ideation, additional follow-up may be completed as per Investigator discretion.
Rationale for change		DMC Recommendation
Section to be changed		Inclusion Criteria
Description of change		Footnote added to inclusion criteria #3: Patients who had a temporary treatment discontinuation during the parent trial, but who restarted treatment and completed the planned EOT on study drug can be considered per investigator judgement
Rationale for the change		Clarification
Section to be changed		Exclusion Criteria
Description of change		Removed the following wording to exclusion criteria #4; the treatment period of trial 1346-0011, 1346-0012 or 1346-0013.
Rationale for change		Clarification as all positive results for urine drug screening are being considered, including follow up visits.

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		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

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

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