Clinical Trial Protocol

Document Number:	**c40079435-01**
EudraCT No.	2022-002739-74
BI Trial No.	1346-0047
BI Investigational Medicinal Product	BI 425809 (iclepertin)
Title	Pharmacokinetics, safety and tolerability of BI 425809 (iclepertin) following oral administration in male and female participants with different degrees of renal impairment (severe, moderate and mild) compared with matched male and female participants with normal renal function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Lay Title	A study to test how iclepertin is taken up in the blood of people with and without kidney problems
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 1.0, 23 November 2022
Original Protocol Date	23 Nov 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	23 November 2022
Revision date	Not applicable
BI trial number	1346-0047
Title of trial	Pharmacokinetics, safety and tolerability of BI 425809 (iclepertin) following oral administration in male and female participants with different degrees of renal impairment (severe, moderate and mild) compared with matched male and female participants with normal renal function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	In this trial, pharmacokinetics, safety, and tolerability of iclepertin single oral dose in participants with different degrees of renal impairment compared to individually matched participants with normal renal function will be assessed.
Trial objective(s)	To investigate the effect of severe, moderate and mild renal impairment on the pharmacokinetics of iclepertin (including its metabolites)
Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of iclepertin Secondary endpoints: $AUC_{0-\infty}$ of iclepertin

Trial design	Open-label, non-randomised, single dose, parallel, individual matched design
Number of participants	
total entered	48* * additional participants may be included to ensure that the study objectives are reached
on treatment	• *Group 1:* 8 participants with severe renal impairment • *Group 2:* 8 participants with normal renal function matching Group 1** • *Group 3:* 8 participants with moderate renal impairment • *Group 4:* 8 participants with normal renal function matching Group 3** • *Group 5:* 8 participants with mild renal impairment • *Group 6:* 8 participants with normal renal function matching Group 5** ** each participant with normal renal function may be matched to multiple renal impaired participants across different groups and can be matched to only 1 renal impaired participant within a group. Thus, the total sample size may be 32 to 48 participants.
Diagnosis	Participants with renal impairment (severe, moderate and mild) and participants with normal renal function (matched controls to the participants with renal impairment)
Main inclusion criteria	Male/female participants (at least 25% of each gender), age of at least 18 years (inclusive), body mass index (BMI) of 18.5 to 35 kg/m^2 (inclusive) with renal impairment (severe, moderate and mild) based on assessment of eGFR: Mild impairment: 60-89 mL/min/1.73m² Moderate impairment: 30-59 mL/min/1.73m² Severe impairment: 15-29 mL/min/1.73m² Participants with normal (≥90 mL/min/1.73m^2) renal function, age of at least 18 years, BMI of 18.5 to 35 kg/m^2 (inclusive) – individually matched by age (± 10 years), gender, weight (± 15%) and race to the participants with renal impairment.
Test product	BI 425809 (iclepertin) film-coated tablet
dose	10 mg
mode of administration	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	Single dose

Statistical methods	To assess the effect of renal impairment on the primary and secondary pharmacokinetic endpoints of iclepertin, the relative bioavailability will be estimated by the ratios of the geometric means of the respective pairwise comparison of interest, i.e., for each renal impairment group vs. the respective control group. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified for any comparison of interest. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including the fixed effect ‘degree of renal impairment’ and the random effect ‘matched pair’. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [8]	PK blood [9]	PK urine [10]	Suicidality assessment [14]	12-lead ECG [11]	Vital signs (BP, PR) [12]	Questioning for AEs and concomitant therapy [6]
1	-21 to -2			Screening (SCR)[1]	A			x	x	x	
2	-1	-24:00	08:00	Admission to trial site	B [5]					x[13,15]	x
	1	-2:00	06:00			x[2]	x[2,7]	x[2]	x[2]	x[2]	x[2,16]
		0:00	08:00	Drug administration			▲				
		0:30	08:30			x	|				
		0:45	08:45			x	|				
		1:00	09:00			x	|		x	x	x
		1:15	09:15			x	|				
		1:30	09:30			x	|				
		1:45	09:45			x	|				
		2:00	10:00	240 mL fluid intake (snack for participants with diabetes)[3]		x	|		x	x	x
		2:30	10:30			x	|				
		3:00	11:00			x	|				
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	┼		x	x	x
		6:00	14:00			x	|				
		8:00	16:00	Snack (voluntary)[3]		x	┼		x	x	x
		10:00	18:00			x	|				
		11:00	19:00	Dinner[3]			|				
		12:00	20:00			x	┼				x
		14:00	22:00			x	|				
	2	24:00	08:00		B	x	┼		x	x	x
		36:00	20:00			x	┼				x
	3	48:00	08:00			x	┼				x
	4	72:00	08:00	Breakfast (voluntary)[3], Discharge from trial site	B	x	┼	x	x	x	x
	5	96:00	08:00	Ambulatory visit		x	┼				x
	6	120:00	08:00	Ambulatory visit		x	▼				x
	7	144:00	08:00	Ambulatory visit		x		x			x
3	12 to 19			End of study (EoS) examination[4]	C			x	x	x	x

r1. Participant must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination (including assessment of suicidal ideation and behaviour using the C-SSRS questionnaire), check of vital signs, ECG, safety laboratory (including drug screening, alcohol breath test, serology, and SARS-CoV-2 PCR test, serum pregnancy test in WOCBP), eGFR, demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.

2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination (including assessment of suicidal ideation and behaviour using the C-SSRS questionnaire), body weight, vital signs, ECG, safety laboratory (including urine pregnancy test in WOCBP), recording of AEs and concomitant therapies.
5. In addition: urine drug screening, alcohol breath test, SARS-CoV-2 antigen test, as well as serum pregnancy test in WOCBP.

6. AEs and concomitant therapies will be recorded throughout the trial but will be specifically asked for at the times indicated in the Flow Chart above.
7. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96 and 96-120 h..
8. Letters A, B and C define different sets of safety laboratory examinations (for details refer to Section 5.2.3).
9. For details of PK blood sampling, refer to Section 5.3.2.1.
10. For details of PK urine sampling, refer to Section 5.3.2.2.
11. For details of 12-lead ECG, refer to Section 5.2.4.
12. For details of vital signs evaluation, refer to Section 5.2.2.
13. Including assessment of body temperature (if needed due to the current status of the pandemic).
14. For details of suicidality assessment, refer to Section 5.2.5.1.
15. Including measurement of body weight at this time point.
16. Before administration of study medication at Visit 2, site staff will remind participants to report “any unusual visual perception they may experience”, refer to Section 5.2.6.1.5.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

$\%AUC_{tz-\infty}$	The percentage of $AUC_{0-\infty}$ obtained by extrapolation
^{14}C	Radiocarbon
AE	Adverse event
AESI	Adverse event of special interest
Ae_{t1-t2}	Amount of analyte that is eliminated in urine from the time interval t_1 to t_2
ALCOA	Attributable, legible, contemporaneous, original, and accurate
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AV	Atrioventricular
BI	Boehringer Ingelheim
Bid	Twice daily (bis in die)
BMI	Body-mass index
BP	Blood pressure
CI	Confidence interval
CIAS	Cognitive impairment associated with schizophrenia
CL	Clearance
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
COVID-19	SARS-CoV-2 induced disease
CRF	Case report form
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction

DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EoS	End of study
EudraCT	European union drug regulating authorities clinical trials database
[redacted]	[redacted]
Fpo	Oral bioavailability
GCP	Good clinical practise
GlyT1	Glycine transporter 1
GMP	Good manufacturing practice
HbA1c	Glycated haemoglobin
HR	Heart rate
IB	Investigator brochure
IMP	Investigational medicinal product
IPD	Important protocol deviation
IRB	Institutional review board
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
K_2-EDTA	Dipotassium ethylenediaminetetraacetic acid
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple rising dose
MRT_{ex}	Mean residence time of the analyte in the body after extravascular administration
NMDA	N-methyl-D-aspartate
NSFS	Negative Symptom Factor Score
PANSS	Positive and Negative Syndrome Scale
PE	Polyethylene
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
PP	Polypropylene
PR	Pulse rate
PT	Preferred term
Qd	Once daily (quod diem)

QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
QWBA	Quantitative whole-body autoradiography
REP	Residual effect period
RI	Renal impairment
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SRD	Single rising dose
[redacted]	[redacted]
TS	Treated Set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual analogue scale
V_{ss}	Volume of distribution
[redacted]	[redacted]
WOCPB	Women of childbearing potential
[redacted]	[redacted]

1. INTRODUCTION

Iclepertin (BI 425809) is a glycine transporter 1 (GlyT1) inhibitor under development for treatment of cognitive impairment associated with schizophrenia (CIAS).

1.1 MEDICAL BACKGROUND

Schizophrenia is a chronic, severe, and disabling brain disorder affecting both men and women. The disease is characterised by abnormalities in glutamatergic pathways related to N-methyl-D-aspartate (NMDA) receptor hypofunction in cortical and hippocampal brain areas [R13-4518, R13-4521]. These abnormalities are hypothesised to lead to negative symptoms and cognitive impairment in schizophrenia. Existing treatment options for schizophrenia (i.e. first- and second-generation antipsychotics) primarily affect positive symptoms but have a limited effect on cognitive and negative symptoms [R15-0595].

[redacted]

1.2 DRUG PROFILE

[redacted]

bioavailability (Fpo). In studies with Caco-2 cell monolayers, the permeability of iclepertin is high.

Based on mass balance and metabolite identification studies, the CL of iclepertin occurs primarily by metabolism, as only low amounts of unchanged iclepertin are found in excreta. Metabolism of iclepertin in mouse, rat, and minipig was determined to be principally oxidative. In a quantitative whole-body autoradiography (QWBA) study in the pigmented rat, where ^{14}C iclepertin was administered orally, radioactivity extensively distributed into tissues, including the CNS. There was no preferential binding of radioactivity to melanin. In pregnant rats, orally administered ^{14}C iclepertin, radioactivity was moderately distributed into the placenta, embryo and foetus. Higher exposure to ^{14}C iclepertin-related radioactivity was observed in the CNS and eye of the foetus relative to the respective maternal organs. In lactating rats administered a single oral dose of ^{14}C iclepertin, ~16% of dosed radioactivity was excreted into milk.

Metabolite profiling and identification was performed in clinical trial 1346.0016 [n00277070]. Twenty-one metabolites of iclepertin were identified including two major plasma metabolites, [redacted]. Neither [redacted] possesses pharmacological activity toward GlyT1, GlyT2 or 102 off-target receptors, and no evidence of genotoxicity, effects on embryo-foetal development, or adverse effects has been revealed in repeat-dose toxicity studies.

Excretion

In CD-1 mice, Wistar Han rats, and Göttingen minipigs, the major route of excretion of radioactivity from ^{14}C iclepertin was in faeces. For male and female CD-1 mice, 82 and 77% of the radioactive dose, respectively, was accounted for in the faeces [n00273967]. For male and female Wistar Han rats, 91.3 and 86.4% of the radioactive dose, respectively, was accounted for in the faces [n00237515]. For Göttingen minipigs, 72% of the radioactive dose (average of male and female) was accounted for in the faeces [n00243611]. In all species administered a single oral dose of ^{14}C iclepertin, drug-related radioactivity was primarily excreted as metabolites. In humans, 45.9% of the radioactive dose of iclepertin was excreted in the faeces and 41.3% of the dose was excreted in the urine [c26534937]. Excretion of unchanged iclepertin in human was <10% in urine and <1% in faeces.

For details on the non-clinical pharmacology, PK in animals and toxicology of iclepertin please refer to the current IB [c02155957].

1.2.1.2 Clinical safety in healthy subjects

In total and up to the data lock point for the current IB, 323 healthy participants have received ≥1 dose of iclepertin, including 265 males (82.0%) and 58 females (18.0%). Safety data below were pooled from 12 Phase I clinical trials with healthy participants (trials 1346.1/.2/.3/.4/.10/ .15/.16/.18/.19/.22/.29/.39); see IB [c02155957] or respective clinical trial reports.

Iclepertin was administered in single doses ranging from 0.5 mg to 150 mg qd, or multiple doses ranging from 5 mg to 75 mg bid (i.e. a maximum of 150 mg/day) for a maximum of

14 days. No deaths or serious adverse events (SAEs) were reported, and no AEs of special interest (AESIs) were observed. No ethnic pattern of AEs was observed.

Severe AEs were reported for 3 participants (0.9%): neck pain (trial 1346.3; 10 mg; not drug-related [c03724403]), nausea (trial 1346.10; 25 mg; drug-related [c03355329]), and vomiting (1346.1; 150 mg; drug-related [c02820512]) each in 1 participant. Investigator-defined drug-related AEs were reported for 37.2% of participants treated with iclepertin versus 26.9% of participants on placebo.

Most frequent AEs in iclepertin treatment groups were (on the preferred term (PT) level):

- Headache 20.4% vs. 9.6% in the pooled placebo group
- Dizziness 10.2% vs. 5.8% in the pooled placebo group
- Fatigue 8.4% vs. 5.8% in the pooled placebo group
- Nausea 7.4% vs. 1.9% in the pooled placebo group
- Nasopharyngitis 5.6% vs. 5.8% in the pooled placebo group
- Back pain 5.3% vs. 3.8% in the pooled placebo group
- Vomiting 5% vs. 1.9% in the pooled placebo group
- Procedural headache 5.0% vs. 0% in the pooled placebo group
- Vision blurred 3.4% vs. 0% in the pooled placebo group
- Diarrhoea 3.1% vs. 1.9% in the pooled placebo group
- Oropharyngeal pain 2.5% vs. 1.9% in the pooled placebo group

AEs leading to discontinuation were reported by 4 participants on iclepertin:

- 1 participant receiving 5 mg iclepertin qd experienced nausea and vomiting of moderate intensity, both not considered drug-related (trial 1346.3, [c03724403])
- 1 participant receiving 10 mg iclepertin qd experienced procedural headache (CSF sampling) of moderate intensity not considered drug-related (trial 1346.3, [c03724403])
- 1 participant receiving 25 mg iclepertin qd experienced diarrhoea of moderate intensity not considered drug-related (trial 1346.39, [c30032912])
- 1 elderly (aged 66 years) female participant receiving 50 mg iclepertin qd experienced nausea of moderate and vomiting of mild intensity after the 1st dose, both considered drug-related (trial 1346.2, [c03572014])

In general, there were no clinically relevant findings in the clinical laboratory evaluation, 12-lead ECG, or vital signs. No suicidal ideation or behaviour was observed.

Clinical pathology findings in repeat-dose studies in mice, rats and minipigs included changes in red blood cell indices. Findings, generally, included reductions in haemoglobin (Hb), haematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and/or mean cell haemoglobin concentration (MCHC) and increases in RBC count, red cell distribution width (RDW), platelets and/or absolute reticulocytes. In the Phase II trials in patients with schizophrenia and Alzheimer's disease, after 12-week treatment with iclepertin a dose-dependent decrease in haemoglobin was noted at doses of 10 mg (-2.3%) and 25 mg (-3.2%) at last value on treatment as compared to baseline [c31477880].

In trials with healthy volunteers, no notable decrease in haemoglobin or haematocrit was noted in the iclepertin treatment groups compared with placebo.

In the single rising dose study (1346.1) using powder as solution formulation, dose-related increases in Bond-Lader and Bowdle visual analogue scale (VAS) scores were observed [c02820512]. An increase in VAS scores for drowsiness and AEs of somnolence were observed with dose-dependency. At high doses (100 to 150 mg), i.e., much higher than the expected efficacious dose (10 mg tablet formulation), increases in VAS scores related to perception were observed. Additionally, visual disturbances were noted in the 2 highest dose groups (1 case of blurred vision in the 100 mg dose group, and all subjects in the 150 mg group had visual disturbances, including photopsia, blurred vision, and chromatopsia). On ophthalmologic testing, no abnormality was noted on visual acuity or colour vision, but abnormalities on the Amsler grid test were noted in 2 subjects (25 and 100 mg). The effects peaked around t_{max}. The frequency of ophthalmologic AEs was comparable in iclepertin and placebo groups in all trials using the tablet formulation.

In the multiple rising dose study (1346.2, [c03572014] multiple doses of 10 mg, 25 mg, 50 mg and 75 mg were investigated. The following drug-related AEs were reported by healthy young participants in Part I of 1346.2, [c03572014]:

- 10 mg qd: headache (2x), dizziness (1x), head discomfort (1x), nasal dryness (1x)
- 25 mg qd: blurred vision (2x), headache (2x), abdominal discomfort (2x), abdominal pain (2x), nausea (1x), diarrhoea (1x), visual impairment (1x), sleeping disorders (1x)
- 50 mg qd: headache (2x), dizziness (1x), blurred vision (1x), visual impairment (1x), blepharospasmus (1x), folliculitis (1x), feeling cold (1x), gait disturbances (1x)
- 75 mg qd: headache(4x), dizziness (3x), hypoacusis, constipation, vomiting, fatigue (1x each)
- 75 mg bid: insomnia (3x), dizziness (2x), ocular discomfort (2x), reduced visual acuity (1x), transiently reduced visual acuity (1x), eye pain (1x), nervousness (1x), micturition urgency (1x), feeling drunk (1x), gait disturbances (1x)

Visual disturbances occurred only in higher dose groups (25 mg, 50 mg, 75 mg). Most cases started in the first week of treatment, were of short duration (up to 3 days) and resolved prior to the end of dosing. All cases of visual disturbance were of mild intensity. The 2 cases of gait disturbances occurred on Day 1 and were accompanied by dizziness on the same day.

All drug-related AEs were of mild or moderate intensity and resolved by end of the trial. There were no notable changes in lab values, vital signs and ECG parameters after multiple doses of iclepertin [c03572014].

In trial 1346.22 (DDI study with a cocktail of sensitive CYP substrates) 25 mg iclepertin were given for 14 days to healthy male participants. The most frequent drug related AEs were headache (25% of participants) and fatigue (33% of participants). Visual disturbances have not been reported in this trial. The evaluation of visual function tests, safety laboratory values, vital signs, and ECG recordings revealed no clinically relevant findings [c08949593].

1.2.1.3 Clinical pharmacokinetics in healthy subjects

Initially, pharmacokinetics of iclepertin were investigated after dosing of 0.5 to 150 mg iclepertin administered as oral solution in the single rising dose (SRD) part of trial 1346.1 [c02820512]. The drug was rapidly absorbed with median t_{max} values of approximately 45 min after drug administration for all dose groups; individual values ranged from about 30 min to 90 min. The gMean plasma C_{max} values ranged from 10.0 nmol/L to 2970 nmol/L for the 0.5 mg and 150 mg dose groups. The gMean $AUC_{0-\infty}$ values ranged from 187 nmol·h/L to 48500 nmol·h/L for the 0.5 mg and 150 mg dose groups. A linear dose-exposure relationship was evident for the complete dose range. The gMean values of $t_{1/2}$ were independent of the administered dose and ranged from 32.5 h to 47.0 h.

After administration of iclepertin tablets, maximum plasma concentrations of iclepertin occurred around 3 to 4.5 h after dosing. The terminal half-life was independent of the administered dose and ranged from 37 to 59 h. Food increased drug exposure (fed/fasted ratio for C_{max}: 142%, for AUC_{0-tz}: 126%). The absolute bioavailability of iclepertin is about 70%. The orally administered drug is eliminated via renal and foecal route at comparable amounts.

The amount of iclepertin excreted in urine increased with dose, but the gMean fractional renal excretion remained almost the same over all dose groups and was low (around 5%) across all doses.

In the multiple rising dose (MRD) trial 1346.2 [c03572014], after qd dosing for 14 days of 10 to 75 mg iclepertin once or twice daily administered as tablets, steady state was reached after 6 days of dosing with accumulation ratios for C_{max} ranging from 1.96 to 2.63 and for AUC from 2.31 to 3.21.

In the current trial, iclepertin 10 mg will be given as a single dose on Day 1 of Visit 2. In the trial 1346.2 [c03572014], a half-life of 45.2 h was reported for the 10 mg dose group under steady state conditions, maximum plasma concentrations were achieved after 4.5 h [c02155957].

Metabolite profiling and identification was performed using plasma, urine, and faecal samples collected from healthy human volunteers receiving a single oral dose of ^{14}C iclepertin (25 mg) in clinical trial 1346.0016 [n00277070]. In plasma, iclepertin (41.0%) and its two major metabolites, [redacted] (34.3%) and [redacted] (11.9%), accounted for 87.2% of total radioactivity (AUC_{0-168}). BI 758790 showed its C_{max} of 138 nmol/L at a median t_{max} of 10.0 h, [redacted] appeared later with a median t_{max} of 192 h and C_{max} of 55.6 nmol/L. The AUC_{0-tz} showed a comparable plasma exposure for iclepertin and its metabolite [redacted], whereas the AUC_{0-tz} for [redacted] was about 2-fold higher in comparison. Similar results were received for $t_{1/2}$. The half-lives of iclepertin and [redacted] were with values of 50.5 h and 46.7 h in a similar range, whereas the half-life for [redacted] was clearly prolonged (243 h).

1.2.1.4 Pharmacokinetic drug interactions

In vitro studies were conducted to assess the potential for iclepertin or its major metabolites to cause clinically relevant DDIs via inhibition or induction of major drug metabolising enzymes or inhibition of major drug transporters. Results from *in vitro* metabolism studies indicate that iclepertin is primarily metabolised by hepatic CYP3A. Furthermore, CYP3A plays a major role in the *in vivo* clearance of iclepertin based on clinical DDI studies.

Results from preclinical studies indicate that iclepertin and the metabolite [redacted] may cause clinically relevant induction and inhibition of CYP3A. However, in a clinical DDI study (1346.22; [c08949593]), inhibition of CYP3A was not observed.

In clinical studies, iclepertin has been characterised to be a substrate of CYP3A4. Itraconazole, a recommended inhibitor of CYP3A4, increased the $AUC_{0-\infty}$ of iclepertin by factor 6 [c03355329]. Rifampin, a recommended inducer of CYP3A4, decreased C_{max} and AUC of iclepertin by 63% and 90% [c18001523].

In trial 1346.22 [c08949593], the clinical effect of iclepertin on sensitive substrates of CYP3A4 (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole) and P-glycoprotein (digoxin) was investigated. Multiple doses of 25 mg iclepertin did not change the exposure of S-warfarin and digoxin but caused a reduction of midazolam by 22% for C_{max} and by 29% for AUC_{0-tz} indicating for (mild) induction of CYP3A4. Exposure to the other investigated substrates seemed to be not relevantly affected. [c08949593]. Currently, a dose of 10 mg qd of iclepertin is the proposed therapeutic dose in clinical development.

For a more detailed description of iclepertin please refer to the current IB [c02155957].

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of iclepertin is [redacted] This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

In this trial, PK of iclepertin single oral dose in participants with different degrees of renal impairment compared to individually matched participants with normal renal function will be assessed.

Iclepertin is being developed for the treatment of CIAS.

This exploratory trial is designed to investigate the effect of mild, moderate, and severe renal impairment on the PK, safety and tolerability of iclepertin and its metabolite. The data obtained in this trial will provide a basis for the treatment of patients suffering from CIAS with renal impairment.

The design of this trial follows the FDA draft guideline for Industry "Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function –Study Design, Data Analysis, and Impact on Dosing" [R22-3783] and the EMA "Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function" [R22-3784].

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for the participants. Their participation, however, is of major importance for the development of iclepertin which may help to treat patients suffering from CIAS.

1.4.2 Risks

Participants are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table 1.4.2: 1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: iclepertin		
CNS-related effects	CNS depressant effects indicated by nonclinical data, and also observed in clinical studies with other compounds in the same pharmacological class [R13-4450]*R13-4450.* In clinical studies with healthy volunteers, headache, dizziness and fatigue were the most frequently reported AEs in iclepertin treatment groups. For details refer to Section 1.2.1.11.2.1.1, and the current IB [c02155957].	In case of headache, the investigator may initiate symptomatic treatment if deemed necessary. Participants will be asked to use public transport instead of driving cars and not to operate machines should they experience CNS-related effects that might impair ability to drive or operate machines. In questionable cases neurological tests and testing of driving ability prior to discharge will be initiated by the investigator. In-house stay may be prolonged at any time at the discretion of the investigator. Alcohol is not permitted from 7 days before the drug administration until the last PK sample.
Psychiatric disorders: Suicidality	In clinical studies, no signal for suicidal ideation or behaviour was observed.	Prospective monitoring for suicidal ideation behaviour using the C-SSRS. The risk after a single administration of iclepertin is considered low and will be addressed by careful close clinical monitoring for AEs and increased awareness by the investigator for signs and symptoms of depression and anxiety as well as for signs and symptoms of suicidal ideation and behaviour. Only participants with no relevant medical history including psychiatric disorders will be enrolled. Any suicidal behaviour in the past 2 years and any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1 are exclusion criteria. Patient's withdrawal criteria in case of new-onset suicidal behaviour or any suicidal ideation of type 4 or 5 in the C-SSRS.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Gastrointestinal effects	In clinical studies with healthy volunteers, nausea, vomiting and diarrhoea were among the most frequently reported AEs in iclepertin treatment groups. For details refer to Section 1.2.1.11.2.1.1, and the current IB [c02155957].	Clinical gastrointestinal symptoms will be monitored carefully, and symptomatic treatment may be initiated by the investigator if deemed necessary (e.g. fluid replacement in case of diarrhoea).
Ophthalmological effects	In the single rising dose trial using powder for oral solution formulation (1346.1 [c26534937]), dose-related increases in VAS scores and visual disturbances (blurred vision, photopsia, chromatopsia) were observed around t_{max} [c02820512]. For details refer to the current IB [c02155957].	Participants will be advised not to drive cars or operate machines should they experience blurred vision. In questionable cases visual tests will be initiated by the investigator. In-house stay may be prolonged at any time at the discretion of the investigator. In case of ophthalmological AEs, evaluation to be made by an ophthalmologist (see Section 5.2.6.1.5).
Haematology changes	Changes in red blood cell parameters (reductions in haemoglobin, haematocrit, etc.) indicated by nonclinical data. In trials with healthy volunteers, no notable decrease in haemoglobin or haematocrit was noted in the iclepertin treatment groups compared with placebo. A dose-dependent decrease in haemoglobin was noted in the longer term 12-week Phase II trials with patients at doses 10 mg (-2.3%) and 25 mg (-3.2%) at last value on treatment as compared to baseline. For details refer to Section 1.2.1.1, and the current IB [c02155957].	Participants will regularly undergo clinical laboratory testing to monitor potential iclepertin induced alterations. Administration of iclepertin is limited to a single dose of 10 mg iclepertin.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

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 participants' safety.
Drug-drug interaction between iclepertin and other drugs	Co-administration with a strong CYP3A inhibitor increased the total exposure of iclepertin significantly, while it was significantly decreased in the presence of a strong CYP3A4 inducer (for details refer to the current IB[c02155957]).	Participants will not be allowed to use strong and moderate inhibitors or inducers of CYP3A4 (see Appendix 10.2) within 30 days before start of trial treatment.
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site

The total volume of blood withdrawn per participant during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to participants of this trial is expected from withdrawal of this volume of blood.

Consideration on male contraception requirements

Contraception for male clinical trial participants with sexual partners who are WOCBP, and the collection of pregnancy information from sexual partners of male clinical trial participants, are not required in clinical trials with iclepertin.

Considerations on female contraception requirements, pregnancy, and lactation

Iclepertin may be administered to WOCBP with a medically acceptable method of contraception (see Section 3.3.2).

Iclepertin should not be used during pregnancy and use should be discontinued upon confirmation of pregnancy. Iclepertin must not be administered to women who are, or who may be, breastfeeding.

Considerations on COVID-19

Generally, for participants of this trial, the risk of severe COVID-19 infection is not higher, and study participation would not increase the risk of becoming infected with SARS-CoV-2 beyond the potential risk associated with any need for the study participant to leave their home for study related activities. The appropriate risk minimisation measures will be taken in accordance with the public health precautions if needed due to the current status of the pandemic (e.g. minimising time at the clinic, minimising the use of public transportation to the site). The investigators will take the totality of information related to each single participants 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 participant's (continued) participation in the trial.

Of note, depending on the current status of the COVID-19 pandemic, all participants with confirmed SARS CoV-2 infection will be handled in accordance with local guidance and SOPs meaning that any confirmed SARS CoV-2 infection during the conduct of the trial will lead to discontinuation of the participant.

1.4.3 Discussion

The nature of the target and the mechanism of action of iclepertin is well understood. The safety profile of iclepertin has been characterized in several clinical trials including the administration to more than 300 healthy subjects so far. After single dosing, iclepertin up to 50 mg was safe and well-tolerated, but higher doses showed increased incidences of AEs and the occurrence of sedative effects and perceptual alterations. In line with its mode of action, drug related AEs after multiple dosing of iclepertin to healthy subjects have a CNS focus and include headache, fatigue, dizziness, visual disturbances (blurred vision, reduced visual acuity) and gait disturbances. All these AEs were manageable within the setting of a phase I trial, did not jeopardise the subject`s safety and resolved by end of the trial.

In the current trial, adequate safety monitoring including vital signs, ECG, C-SSRS, safety laboratory and AE monitoring has been implemented.

Taking into account these safety measures, potential risks to participants with normal renal function and those impaired renal function are considered to be low and outweighed by the benefit of a successful clinical development of iclepertin in the context of the unmet medical need.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the effect of severe, moderate and mild renal impairment on the PK of iclepertin following oral administration.

2.1.2 Primary endpoints

The following PK parameters will be determined for iclepertin:

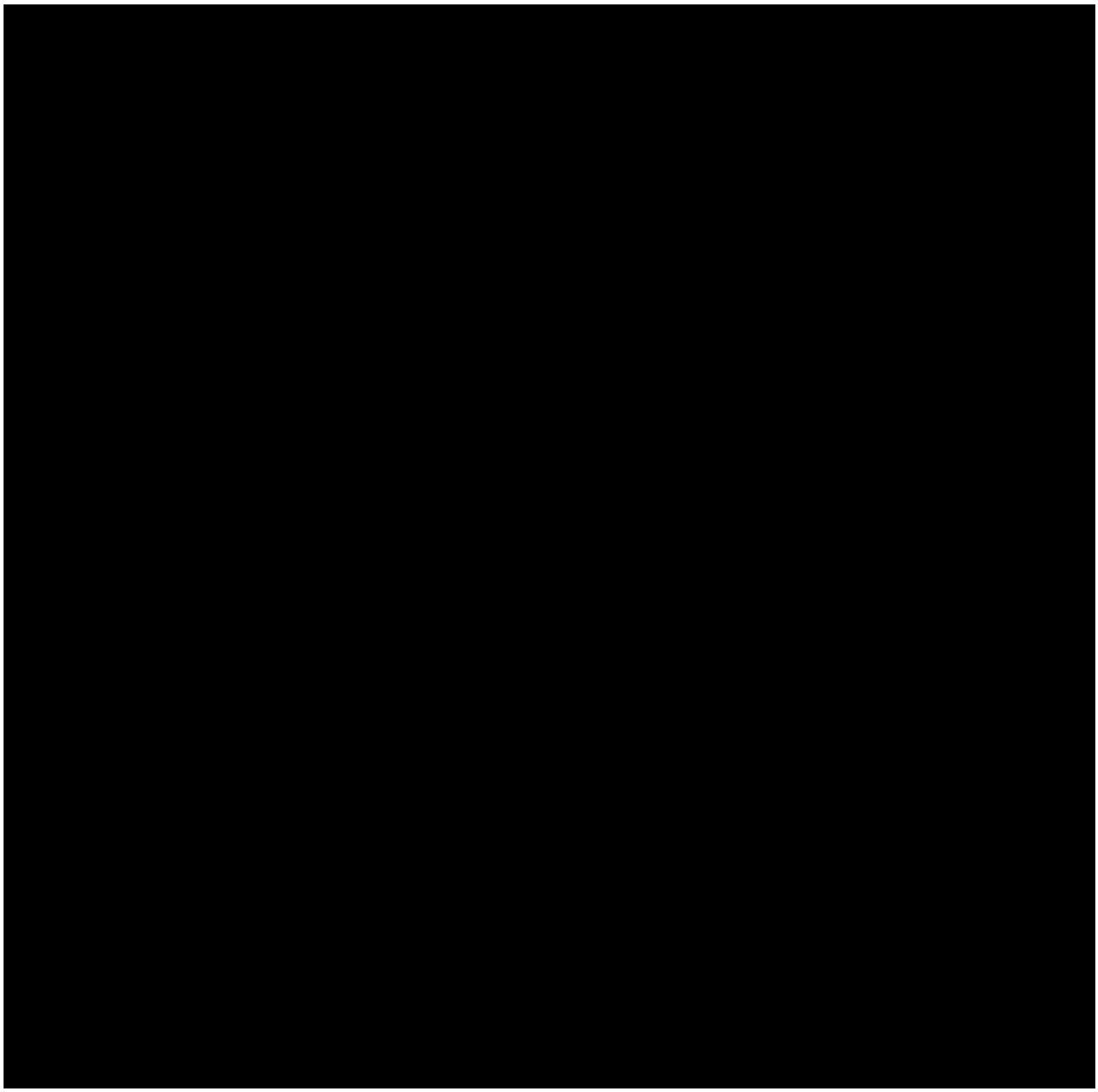
- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of iclepertin in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of iclepertin in plasma)

2.1.3 Secondary endpoint

The following PK parameter will be determined for iclepertin:

- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

[redacted]



2.2.2.3 Safety and tolerability

Safety and tolerability of iclepertin will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- Assessment of suicidal ideation and behaviour (C-SSRS)
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a non-randomised, single dose, open-label, parallel, individual-matched design in order to investigate the PK of iclepertin (and its metabolites), as well as the safety and tolerability of iclepertin in severe, moderate, and mild renal impaired male and female participants compared to matched participants with normal renal function.

The treatment will be one 10 mg tablet administered to participants in the fasting state. For details, refer to Section 4.1.

The trial will be performed in 6 groups:

- Group 1: 8 participants with severe renal impairment (eGFR at screening 15-29 mL/min/1.73 m^2)
- Group 2: 8* participants with normal renal function individually matched to participants of Group 1 (eGFR at screening ≥90 mL/min/1.73 m^2)
- Group 3: 8 participants with moderate renal impairment (eGFR at screening 30-59 mL/min/1.73 m^2)
- Group 4: 8* participants with normal renal function matching Group 3 (eGFR at screening ≥90 mL/min/1.73 m^2)
- Group 5: 8 participants with mild renal impairment (eGFR at screening 60-89 mL/min/1.73 m^2)
- Group 6: 8* participants with normal renal function matching Group 5 (eGFR at screening ≥90 mL/min/1.73 m^2)

*Each participant with normal renal function may be matched to multiple participants with renal impairment across groups and can be matched to only 1 participant within a renal impairment group.

Each group will contain at least 25% participants (i.e., 2) of each gender.

Matching criteria of the participants with normal renal function to the participants with renal impairment:

- Age (± 10 years)
- Gender
- Race
- Weight (± 15%)

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

Definitions of trial start and end are given in Section 8.6.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The defined single-dose individual-matched comparison is deemed appropriate to meet the objectives of the study.

From preclinical and clinical data (see Section 1.2.1), no clinically relevant increase in exposure to iclepertin in participants with impaired renal function is expected.

The single dose of 10 mg of iclepertin selected in this trial is the currently expected therapeutic dose and has been considered as safe for the trial populations.

The PK of iclepertin are dose-proportional (up to 150 mg in liquid formulation and 25 mg in tablet formulation) and dose-linearity was also shown for 10 mg after multiple doses. Therefore, a 10 mg single dose has been considered sufficient for the planned PK evaluations and adequate to meet the objectives of the trial.

The group size of 8 participants is considered sufficient for the exploratory evaluation of PK. The assignment of individually match participants with normal renal function is a useful method to control for other factors which may influence the PK of iclepertin in a renal impaired population.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma and urine concentrations of the analyte. Furthermore, all participants will receive the same dose, and participants will be stratified to the groups according to their renal function.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 24 male and female participants with severe, moderate, or mild renal impairment (at least 25% of each gender per group) and up to 24 male and female control participants with normal renal function (Groups 2, 4, and 6) will enter the trial.

The participants with normal renal function will be recruited from the volunteers' pool of the trial site. The participants with renal impairment will be recruited in cooperation with different nephrological centres who primarily diagnose the underlying medical condition leading to chronic renal impairment.

The participants will be assigned to one of the renal function groups (severe, moderate, and mild impairment, normal renal function) based on their eGFR according to CKD-EPI (see Appendix 10.3). In addition, participants with normal renal function will be assigned to a group according to their match to a participant with renal impairment (3.3: 1).

Table 3.3: 1 Overview of group stratification

Group	Renal function	eGFR (mL/min/1.73 m^2)	Number of participants
1	Severe impairment	15 – 29	8
2	Normal renal function	≥90	up to 8*
3	Moderate impairment	30 – 59	8
4	Normal renal function	≥90	up to 8*
5	Mild impairment	60 – 89	8
6	Normal renal function	≥90	up to 8*

* Each participant with normal renal function may be matched to multiple participants with renal impairment across groups and can be matched to only 1 participant within a renal impairment group

Participants with normal renal function will be matched individually to a participant with impaired renal function by gender, race, age (within ±10 years) and weight (within ±15%) to 1 participant with renal impairment. One participant with normal renal function may be matched to multiple participants with renal impairment across different groups and can be matched to only 1 participant with renal impairment within a group.

Please refer to Section 4.1.3 regarding the method of assigning participants to treatment groups.

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in participants with renal impairment (severe, moderate and mild) and participants with normal renal function (matched controls to the participants with renal impairment).

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

3.3.2 Inclusion criteria

3.3.2.1 Inclusion criteria applicable to all participants

Participants will only be included in the trial if they meet the following criteria:

1. Male or female participants
2. Age of at least 18 years (inclusive)
3. BMI of 18.5 to 35 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

5. Male participants are not required to use contraception
6. WOCBP are allowed to participate provided they use a highly effective contraception from at least 30 days before the administration of trial medication until 30 days after trial completion.
   The following methods of contraception are considered adequate for female participants of childbearing potential:

   - Use of combined (oestrogen and progestogen containing) hormonal contraception that prevents ovulation (oral, intravaginal or transdermal), *plus condom*
   - Use of progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants*), plus condom*
   - Use of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
   - Sexually abstinent
   - A vasectomised sexual partner who received medical assessment of the surgical success (documented absence of sperm) and provided that partner is the sole sexual partner of the trial participant.

   Female participants are not considered to be of childbearing potential if they are either surgically sterilised (including hysterectomy) or postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 40 U/L and oestradiol below 30 ng/L is confirmatory).

3.3.2.2 Inclusion criteria applying only to participants with impaired renal function

In addition to the inclusion criteria given in Section 3.3.2.1, participants with impaired renal function must fulfil the following criteria:

7. Renal impairment based on assessment of eGFR at screening (severe renal impairment: 15-29 mL/min/1.73 m^2, moderate renal impairment: 30-59 mL/min/1.73 m^2, mild renal impairment: 60-89 mL/min/1.73 m^2)
8. Chronic renal impairment > 12 months (documented renal impairment indicated by reduced eGFR for more than 12 months until screening)
9. Absence of clinically significant abnormalities, as based on a complete medical history including a full physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests at both screening and check-in, with the exception of findings that in the opinion of the investigator are consistent with the participant's renal impairment.
10. Medication and/or treatment regimens must have been stable (i.e., no dose adjustments) for at least 4 weeks prior to the screening period and should be kept stable until study completion.
    Fluctuating treatment regimens may be considered for inclusion on a case-by-case

basis if the underlying disease is under control in the opinion of the investigator and must be agreed to by both the investigator and the sponsor's medical monitor.

3.3.2.3 Inclusion criteria applying only to participants with normal renal function

In addition to the inclusion criteria given in Section 3.3.2.1, participants with normal renal function must fulfil the following criteria:

11. Individually matched to participants with renal impairment according to sex, age, and weight, and race
12. eGFR ≥ 90 mL/min/1.73 m^2
13. Absence of clinically significant abnormalities identified by a detailed medical history, full physical examination, vital signs and 12-lead ECG at both screening and check-in visits
14. Absence of clinically significant abnormalities identified by a laboratory test at screening visit

3.3.3 Exclusion criteria

3.3.3.1 Exclusion criteria applying to all participants

Participants will not be allowed to participate, if any of the following general criteria apply:

1. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
2. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the PK of the trial medication (except appendectomy or simple hernia repair)
3. Diseases of the CNS (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders (including but not limited to major depressive disorder)
4. History of relevant orthostatic hypotension, fainting spells, or blackouts
5. Relevant chronic or acute infections
6. 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
7. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
8. Use of drugs within 30 days (or 5 of its half-lives, whichever is longer) of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
9. Intake of an investigational drug in another clinical trial within 60 days (for multiple dose studies) / within 30 days (for single dose studies) or 5 half-lives (whichever is longer) of planned administration of investigational drug in the current trial, or

concurrent participation in another clinical trial in which investigational drug is administered

10. Smoker (more than 15 cigarettes or 5 cigars or 5 pipes per day)
11. Inability to refrain from smoking on specified trial days
12. Alcohol abuse (consumption of more than 10 g per day for females and 20 g per day for males)
13. Drug abuse or positive drug screening
14. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
15. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
16. Inability to comply with the dietary regimen of the trial site
17. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
18. Participant is assessed as unsuitable for inclusion by the investigator, for instance, because the participant is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
19. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection
20. For female participants: Lactation, pregnancy, positive pregnancy test, or plans to become pregnant during the trial or within 30 days after trial completion
21. Any suicidal behaviour in the past 2 years (i.e., actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).
22. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1 and/or Visit 2 predose (i.e., active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan).

3.3.3.2 Exclusion criteria applying only to participants with renal impairment

In addition to the exclusion criteria listed in Section 3.3.3.1, participants with renal impairment fulfilling any of the following criteria will not be included into the trial:

23. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 480 ms in males or repeatedly greater than 500 ms in females) or any other relevant ECG finding at screening
24. Acute renal failure or active nephritis
25. Nephrotic syndrome
26. Impaired hepatic function, including relevant increases in liver enzymes indicating liver disease

27. Relevant diseases for which it can be assumed that the absorption of the study drugs will not be normal (i.e., relevant malabsorption, chronic diarrhoea)
28. Participant under dialysis or planned to start dialysis during participation in the study
29. History of myocardial infarction, cerebrovascular accident or severe arrhythmia within the 6 months prior to the screening visit.
30. History of vascular surgery or intervention (e.g., coronary artery bypass, percutaneous transluminal angioplasty etc.) less than 6 months prior to dosing
31. Congestive heart failure of New York Heart Association grade III or IV, severe arrhythmia requiring antiarrhythmic treatment
32. History of clinically significant aortic or pulmonary valve stenosis, or renal artery stenosis
33. Any other disease or condition which could influence the physiological metabolic turnover (e.g., endocrine diseases, severe infections)
34. Significant uncorrected rhythm or conduction disturbances such as a second-or third-degree AV block without a cardiac pacemaker, QTc prolongation, or episodes of sustained ventricular tachycardia
35. Resting supine systolic BP below 99 or above 179 mmHg and resting supine diastolic BP below 50 or above 100 mmHg at screening visit
36. Resting supine HR equal to or below 50 bpm or above 90 bpm, at screening visit
37. Haemoglobin <9 g/dL
38. Serum albumin <30 g/L
39. Platelet count <100 x 10^9/L
40. Other clinically relevant deviations in clinical chemistry (especially liver enzymes) or haematology
41. Participants with diabetes mellitus with a fasting blood glucose >220 mg/dL or glycated haemoglobin (HbA1c) >10%

3.3.3.3 Exclusion criteria applying only to participants with normal renal function

In addition to the exclusion criteria listed in Section 3.3.3.1, participants with normal renal function fulfilling any of the following criteria will not be included into the trial:

42. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
43. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
44. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg (for participants older than 60 years: 90 to 150 mmHg), diastolic blood

pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm

45. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
46. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Participants may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a participant is removed from or withdraws from the trial prior to the administration of trial medication, the data of this participant will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a participant is removed from or withdraws from the trial after the administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.2, the discontinued participant should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the participant.

3.3.4.1 Withdrawal from trial treatment

An individual participant will be withdrawn from trial treatment if:

1. The participant wants to withdraw from trial treatment. The participant will be asked to explain the reasons but has the right to refuse to answer
2. The participant has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the participant cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The participant needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The participant can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, AEs, or diseases)
5. The participant has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

6. The participant exhibits suicidality, in the clinical judgment of the investigator or according to the following criteria:
   - any suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
   - 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)

In addition to these criteria, the investigator may discontinue participant at any time based on his or her clinical judgment.

If it is known that a participant becomes pregnant during the trial, she is to be removed from the trial. The participant is to be followed until she has given birth or until the end of the pregnancy. The participant's data are to be collected until the end of the trial (last visit of last participant) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.3.

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

3.3.4.2 Withdrawal of consent to trial participation

Participants may withdraw their consent to trial participation at any time without the need to justify the decision. If a participant wants to withdraw consent, the investigator should be involved in the discussion with the participant and explain the options for continued follow-up after trial discontinuation.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, SAEs, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the participants show drug-related and clinically relevant AEs of moderate intensity, or if more than two participants have drug-related severe non-serious AEs, or if at least one drug-related SAE is reported

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5 Replacement of subjects

In case more than 2 participants in a group do not complete the trial (including participants non-evaluable for PK), additional participants may be enrolled and treated in this respective trial group, i.e. ‘replaced‘, if considered necessary to reach the objective of the trial. Participants who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many participants will be replaced. The total number of replacements may not exceed 1/3 of the total number of evaluable participants anticipated to complete the trial. A replacement participant will be assigned a unique trial participant number. In case of enrolment of additional participants, the trial site should ensure the requirements for distribution of gender (‘at least 25% of each gender per group’) are still met within the comprising group of further on treated and additionally enrolled participants.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 425809 (iclepertin)
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	10 mg
Posology:	1-0-0
Mode of administration:	Oral

4.1.2 Selection of doses in the trial

The dose of 10 mg of iclepertin selected for this trial is the therapeutic dose that is used in clinical drug development (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment investigated in this trial.

The participants with renal impairment and the matching participants with normal renal function will be assigned to treatment groups according to their renal impairment based on their eGFR and as control group as outlined in Table 3.3:1.

Once a participant number has been assigned, it cannot be reassigned to any other participants.

All participant within one group may be treated in one cohort, i.e. all participant may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. For discussion of trial-associated risks and safety measures, see Section 1.4).

4.1.4 Drug assignment and administration of doses for each subject

This is a non-randomised, open-label, parallel, individual matched-group design trial. All participants will receive the same active treatment. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	iclepertin	Film coated Tablet	10 mg	1 tablet (10 mg) single dose for 1 day	10 mg

Administration of trial medication will be performed after participants have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to participants who are in a sitting/standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Participants will be kept under close medical surveillance until 48 h after drug administration. During the first 4 h after drug administration, participants are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture), except for assessments and examinations.

4.1.5 Blinding and procedures for unblinding

This non-randomised open-label Phase I trial will be handled in an open fashion throughout. There will be only one treatment, so the treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the participant information form. The EudraCT number is indicated on the title page of this protocol as well as on the participant information and informed consent forms.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial participants. Investigational drugs are not allowed to be used outside of this protocol.

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 participant, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial participants. The investigator or designee will maintain records that document adequately that the participants were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, participants will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed for participants with normal renal function, except for hormonal contraceptives or ovary hormone replacement.

In participants with renal impairment, contraceptives as well as concomitant medication for treatment of the renal or other concomitant diseases are allowed.

Strong CYP3A inhibitors are restricted medication in all trial participants due to potential DDIs (see Appendix 10.2). See also Section 3.3.3 for excluded medication. If necessary, short-term use of ibuprofen or acetylsalicylic acid is acceptable for symptomatic treatment of AEs.

All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the participants will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake. Only participants with diabetes will receive a snack at 2 h post dose, if necessary.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all participants). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements are not permitted from 7 days before administration of trial medication until after the last PK sample of each trial period is collected.

Products containing St. John's wort (*Hypericum perforatum*) are not permitted from 30 days before the administration of trial medication until after the last PK sample is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 24 h before administration of trial medication until the end of in-house confinement at the trial site.

Smoking is not allowed during from 10 h before until 8 h after administration of trial medication.

Excessive physical activity (such as competitive sport) should be avoided from 7 days before administration of trial medication until the end of trial examination.

4.2.2.3 Contraception requirements

If WOCBP are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations and/or urinary excretion of trial medication will provide additional confirmation of compliance.

Participants who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, C-SSRS, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination.

At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination including determination of body weight, recording of AEs and concomitant therapies, and C-SSRS scale.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor ([redacted], [redacted]) at the times indicated in the Flow Chart, after participants have rested for at least 5 min in a supine position. All recordings should be made using the same type of BP recording instrument on the same arm, if possible.

Body temperature will be monitored as part of vital signs assessment if still needed due to the current status of the pandemic. Body temperature will not be entered into the eCRF.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the participants have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
	HbA1c (in diabetic participants only)	X	--	--
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	X
	Prothrombin time	X	--	X
	Prothrombin time – INR (International Normalisation Ratio)	X	--	X
	Fibrinogen	X	--	--
Enzymes	AST (Aspartate aminotransferase) /GOT, SGOT	X	X	X
	ALT (Alanine aminotransferase) /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X
	Creatine Kinase (CK)	X	X	X
	Creatine Kinase Isoenzyme MB (only if CK is elevated)	X	X	X
	Lactic Dehydrogenase	X	X	X
	Lipase	X	X	X
	Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	Free T3 - Triiodothyronine	X	--	--
	Free T4 – Thyroxine	X	--	--
	FSH (if applicable)	X	--	--
	Oestradiol (if applicable)	X	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	Albumin	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	X	X
	Cholesterol, total	X	X	X
	Triglyceride	X	X	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Chloride	X	X	X
	Calcium	X	X	X
	Phosphate (as Phosphorus, Inorganic)	X	X	X
	Magnesium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes or nitrite are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day -1, 2 and 4 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in WOCBP will be performed at screening, prior to treatment, and as part of the end of trial examination. Drug screening will be performed at screening and prior to treatment.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Pregnancy test (serum at screening and Day -1 and urine at EoS)	Beta human chorionic gonadotropin (beta-HCG)
COVID-19 (nasopharyngeal swab)	SARS CoV-2 PCR test (screening) and antigen test on Day -1

To encourage compliance with alcoholic restrictions, a breath alcohol test ([redacted] will be performed prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of drug screening, urine pregnancy tests. The urinalysis (Stix) will be performed with the Combur Test. These tests will be performed at the trial site using Drug-Screen Multi 10TC Urine (distributed by [redacted]) and meditrol hCG, urine test stripe (distributed by [redacted], respectively, or comparable test systems.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to 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 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, [redacted]) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all participants are at complete rest.

All ECGs will be recorded for a 10 sec duration after participants have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the participant will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment

Prospective monitoring will be conducted throughout this trial using C-SSRS.

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behaviour and ideation.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the ‘screening/baseline’ version) with the aim to exclude participant’s suicidal ideation type 4 to 5 within the preceding 3 months or at Visit 1 or any suicidal behaviour in the past 2 years. The lifetime history of suicidal ideation and behaviour will also be recorded.

After Visit 1, the assessment ‘since last visit’ will be performed at each clinic visit (‘since last visit’ version).

Appendix 10.1 provides details how the C-SSRS will be assessed.

C-SSRS results will be reported in terms of AEs as described in Section 5.2.6.2.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An adverse event (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 considered related or not.

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

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

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

<u>SAE reporting in case of suicidal risk assessed by the C-SSRS</u>

All C-SSRS reports of suicidal ideation type 4 and 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator.
For 'self-injurious behaviour, no suicidal intent' (type 11) standard AE/SAE reporting rules are to be applied.
For each negative report (Suicidal ideation type 1, 2, or 3) after the start of the trial, the investigator is to decide based on clinical judgement whether it represents an AE as defined in the CTP, and if it is considered an AE then it must be reported accordingly.

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in

the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. 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 must be classified as a serious event regardless of the time since discontinuation of the trial medication 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 Adverse events of special interest

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

The following are considered as AESIs:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

  These lab findings constitute a hepatic injury alert and the participants 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 that 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.

5.2.6.1.5 Ocular AEs

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

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

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

5.2.6.1.6 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

Infections classified as ‘severe’ are considered as AESIs, see Section 5.2.6.1.4.

5.2.6.1.7 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial 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
- There is an 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

Upon enrolment into a trial, the participant's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Participants will be required to report spontaneously any AEs. In addition, each participant will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, participants will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until an individual participant's end of trial (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when participants discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the participants' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual participant's end of trial:

- The investigator does not need to actively monitor the participant for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On 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 the individual participant's end of trial, must be followed up until they have resolved, have been sufficiently characterised (e.g. 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 participant 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 Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and Part 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 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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood and urine samples will be collected at the time points / time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of iclepertin, [redacted] concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples should be centrifuged immediately for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. If an immediate centrifugation is not feasible blood samples must be stored on ice until centrifugation. Interim storage on ice should not be longer than 30 min. Two plasma aliquots will be obtained and stored in polypropylene tubes. The aliquots should contain 0.5 mL of plasma. Before pipetting plasma into the PP tubes 10 µL (matches 2%) ortho-phosphoric acid (42.5%) must be added into the tubes. To obtain ortho-phosphoric acid (42.5%) solution, 1 ml ortho-phosphoric acid (85%) will be added to 1 ml deionized water. The resulting ortho-phosphoric acid (42.5%) solution can be stored at approximately 4 to 8 °C. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples and aliquots in ice water or on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -80°C +/- 10°C at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -80°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

5.3.2.2 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (ref. Flow Chart) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 3 L polyethylene (PE) containers and stored at room temperature or at 4 to 8 °C. Participants are told to empty their bladders at the end of each sampling interval.

Due to the known adsorption of the drug (its metabolites) to the container wall, 0.5% of a 10% Tween 20 solution will be added to each material prior to the start of urine sampling that urine contact first (3 L PE collection container, collections cup, or whatever). For example, 15 ml of 10% Tween 20 solution to be added to a 3 L urine collection container. The weight of the empty container will be determined, 0.5% of 10% Tween 20 will be added, and the weight of the container at the end of each sampling interval will be determined. Two 0.5 mL aliquots will be stored in PP tubes for bioanalytical measurements. If more than one collection container is used in a sampling interval, the contents of all containers have to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content

of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device made of PE, PP, Teflon, or glass). Generally, the collection container should be shaken upon addition of every urine fraction to ensure proper distribution of Tween and urine.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned collection time.

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at approximately -20°C +/- 5°C at the trial site. The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the urine samples will be stored at approximately -20°C or below until analysis.

After analysis, the urine samples may be used for further methodological investigations (e.g. for stability testing, assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor participants' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, suicidality behaviour, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The PK parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min during the inhouse period, and ± 2 h for ambulatory visits.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the procedures due to its inconvenience to the participant and possible influence on physiological parameters.

For planned blood sampling times and urine collection intervals, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of PK parameters.

To allow for a streamlined operational conduct of trials at trial site, the following flexibility as regards time-windows for PK sampling times will be allowed:

- Predose: within 3 h prior to drug administration
- Postdose:
  - From dosing until 2 h: ± 2 min;
  - >2 h until 4 h: ± 5 min;
  - >4 h until 72 h: ± 15 min;
  - >72:00: ± 60 min

If a participant misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all participants will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, suicidality assessment, and physical examination, refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment period

On Day -1 of the treatment period, trial participants will be admitted to the trial site. They will be kept under close medical surveillance for at least 48 h following drug administration. The participants will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, participants will come to the trial site for ambulatory visits.

For details on time points and procedures for collection of plasma and urine samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining participant's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, suicidality assessment, and physical examination during the follow-up period, see Section 5.2.

Participants who discontinue the trial prematurely should undergo the EoS Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a participant's EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

To assess the effect of renal impairment on the PK of iclepertin, the relative bioavailability will be estimated by the ratios of the geometric means of the respective pairwise comparison of interest for the primary and secondary endpoints, i.e., for each renal impairment group vs. the respective control group. Additionally, their 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all participants who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all participants in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in Section 7.2.1.2). Thus, a participant will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the IPD specification file. IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The PK parameters listed in Section 2.1 and 2.2.2 for drug iclepertin, [redacted] will be calculated according to the relevant BI internal procedures.

Plasma and urine concentration data and parameters of a participant will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a participant's data will be documented in the CTR.

Important protocol deviations may be

- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma and urine concentrations and/or parameters of a participant will be considered as non-evaluable, if for example

- The participant experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the participants experiencing emesis),
- A predose concentration is >5% C_{max} value of that participant
- Missing samples/concentration data at important phases of PK disposition curve

Plasma/urine concentration data and parameters of a participant which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include the effects accounting for 'degree of renal impairment' as a fixed effect as well as 'matched pair' as a random effect. The model is described by the following equation:

$y_{ik} = \mu + s_i + \tau_k + e_{ik}$, where

y_{ik} = logarithm of response measured for the degree of renal impairment k, matched pair i,

μ = the overall mean,

s_i = the effect associated with the i^{th} matched pair (each renal impaired participant with his/her own matched participant with normal renal function), i = 1, 2, ..., 8

τ_k = the effect associated with the k^{th} degree of renal impairment, k = 1 for normal renal function (control) and k=2, 3, 4 for mild, moderate, severe renal impaired respectively,

e_{ik} = the random error associated with the k^{th} degree of renal impairment for matched pair i.

where $s_i \sim N(0, \sigma_B^2)$ i.i.d., $e_{ik} \sim N(0, \sigma_W^2)$ i.i.d. and s_i, e_{ik} are independent random variables (note that the indices 'B' and 'W' correspond to 'between' and 'within' matched pair variability, respectively). The model described above will be fitted separately for the three renal impaired groups, i.e., one model for the participants with mild renal impairment and their matched controls, one model for the participants with moderate renal impairment and their matched controls and one model for the participants with mild renal impairment and their matched controls.

For the evaluation of each primary endpoint, the difference between the expected mean for log response of renal impaired group k (k=2, 3, 4) – log response of normal control group (k=1) will be estimated will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% CIs will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Further exploratory analyses

In addition to the model based approach all parameters will be calculated and analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

[redacted]

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated participants (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

Groups will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to EoS examination date will be assigned to 'follow-up'. These assignments

including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock of the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

C-SSRS results will be reported in terms of AEs as described in Section 5.2.6.2 and will be summarized as such. Results of the C-SSRS will be provided as listing.
Previous and concomitant therapies will be presented per group without consideration of time intervals and treatment periods.

In general, unless otherwise specified in the TSAP, the last non-missing measurement prior to study treatment will be used as baseline for safety variables.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Additionally, differences from baseline will be evaluated.
Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

A preliminary, exploratory analyses of all available or specific data (e.g. safety, PK) may be performed prior to final database lock to inform other activities during the development of iclepertin. In case of preliminary assessment of PK data, the PK parameters will be calculated according to the relevant BI internal procedure. In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The possible preliminary PK analysis will provide individual and gMean concentration profiles and summary statistics of PK parameters per group. No inferential statistical preliminary analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

It is not planned to impute missing values for safety parameters.

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

The trial will not be randomised, thus this section is not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include a maximum of 48 participants in the trial: 8 participants with mild renal impairment, 8 participants with moderate renal impairment, 8 participants with severerenal impairment and up to 24 matched control participants with normal renal function will be treated. Note, one participant with normal renal function may match a participant in only one, two or in all three groups with renal impaired participants. The matching criteria are described in Section 3.1.

The planned sample size is not based on a power calculation but is considered as sufficient to detect major differences between the different groups of participants with renal impairment and the respective control group with participants with normal renal function .

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC 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 will be treated as 'protocol deviation'.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the participant's treating physician.

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

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

The terms and conditions of the insurance coverage are made available to the investigator and the participants and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a participant's participation in the trial, written informed consent must be obtained from each participant 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 participant-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional participant information must be given to each participant.

The participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the participant's own free will with the informed consent form after confirming that the participant 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 participant protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, 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 participants will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial participant that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the participant 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 participant, documented in their medical records, would be acceptable.

Before providing any copy of participants' source documents to the sponsor, the investigator must ensure that all participant identifiers (e.g., participant's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure participant confidentiality.

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject'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)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial subject meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject 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 Clinical Research Associate, 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:
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 SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual subject 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 subject's personal physician or to other appropriate medical personnel responsible for the subject'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, storage and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage 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 (e.g. 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 ICF

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').

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

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

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

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

A final report of the clinical trial data will be written only after all participants have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered 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 participant (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted] under the supervision of the Principal Investigator.

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

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted]

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted]

Analyses of iclepertin, [redacted] concentrations in plasma and urine will be performed at [redacted]

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Data management and statistical evaluation will be done by BI, or a contract research organisation appointed 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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R13-4447 Lane HY, Chang YC, Liu Y, Chiu CC, Tsai GE. Sarcosine or D-serine addon treatment for acute exacerbation of schizophrenia: A randomized, double-blind, placebo-controlled study. Arch Gen Psychiatry 2005. 62:1196-1204.

R13-4450 Liem-Moolenaar, Peeters P, Kamerling C, et al. Early stage development of the glycine re-uptake inhibitor SCH 900435: central nervous system effects compared with placebo in healthy men: Br J Clin Pharmacol 2013; 75(6):1455-1467.

R13-4451 Ouellet D, Sutherland S, Wang T, Griffini P, Murthy V. First-time-inhuman study with GSK1018921, a selective GlyT1 inhibitor: Relationship between exposure and dizziness. Clin Pharmacol Ther 2011; 90(4):597-604.

R13-4508 Martin-Facklam M, Patat A, Hofmann C, et al. Safety, tolerability and pharmacokinetics of RG1678, a novel glycine reuptake inhibitor, after multiple doses in healthy volunteers. Schizophrenia Res 2012. 136(Suppl. 1):S267.

R13-4518 Hu NW, Ondrejcak T, Rowan MJ. Glutamate receptors in preclinical research on Alzheimer's disease: Update on recent advances. Pharmacol Biochem Behav 2012. 100:855-862.

R13-4521 Lin CH, Lane HY, Tsai GE. Glutamate signaling in the pathophysiology and therapy of schizophrenia. Pharmacol Biochem Behav 2012. 100:665-677.

R13-4524 Tsai G, Lane HY, Yang P, Chong MY, Lange N. Glycine transporter I inhibitor, N-methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 2004. 55(5):452-456.

R15-0595 Dunlop J, Brandon NJ. Schizophrenia drug discovery and development in an evolving era: are new drug targets fulfilling expectations? J Psychopharmacol 2015;29(2):230-238.

R15-1266 Umbricht D, Alberati D, Martin-Facklam M, et al. Effect of bitopertin, a glycine reuptake inhibitor, on negative symptoms of schizophrenia: a randomized, double-blind, proof-of-concept study. JAMA Psychiatry 2014; 71(6):637-646.

R18-1054 Bugarski-Kirola D, Blaettler T, Arango C, et al. Bitopertin in negative symptoms of schizophrenia - results from the phase III FlashLyte and DayLyte studies. Biol Psychiatry 2017; 82(1):8-16.

R22-3783 European Medicines Agency. Committee for Medicinal Products for Human use (CHMP): guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (17 December 2015, EMA/CHMP/83874/2014). 2015

R22-3784 Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired renal function - study design, data analysis, and impact on dosing: draft guidance (this guidance document is being distributed for comment purposes only.) (September 2020, clinical pharmacology, revision 2). 2020

R13-4387 Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl; 2013

R12-1392 Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Lente F van, Greene T, Coresh J, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). A new equation to estimate glomerular filtration rate. Ann Intern Med; 2009

9.2 UNPUBLISHED REFERENCES

c02155957 Investigator`s Brochure BI 425809 Alzheimers Disease Cognitive Impairment Associated with Schizophrenia (CIAS). Current version.

c02820512 Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 425809 in healthy male subjects (partially randomised, single-blind, placebo-controlled) and investigation of relative bioavailability and food effect of BI 425809 (open-label, randomised, three-way crossover).1346.1.

c03355329 Relative bioavailability of a single oral dose of BI 425809 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, two-period, fixed sequence trial). 1346.10.

c03572014 Safety, tolerability, and pharmacokinetics of multiple rising doses of BI 425809 tablets given orally once or twice daily for 12 days to young and elderly healthy male and female volunteers (randomised, double-blind, placebo-controlled within dose groups Phase I study) (Part 1) and comparison of pharmacokinetics of a single oral dose of BI 425809 after oral administration in the morning versus oral administration in the evening in young healthy male and female volunteers (randomised, two-sequence, open, two period, two-way cross over) (Part 2). 1346.2.

c03724403 Non-randomised, open label, sequential-group study to assess the pharmacokinetics and pharmacodynamic effect of different multiple oral doses of BI 425809 in healthy male volunteers. 1346.3

c08949593	A study to investigate the effects of multiple doses of BI 425809 on the single dose pharmacokinetics of cytochrome P450 substrates (midazolam, warfarin and omeprazole) and a P-glycoprotein substrate (digoxin) administered orally in an open-label, one-sequence trial in healthy male subjects. 1346.22.
c18001523	Effects of rifampicin on the pharmacokinetics of BI 425809 following oral administration in healthy male subjects (an open-label, two-period, fixed sequence trial). 1346.18.
c26534937	Metabolism and pharmacokinetics of BI 425809 after administration of BI 425809 (C-14) as oral solution in healthy male volunteers. 1346.16.
c30032912	A study to investigator the effects of memantine on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (nonrandomised, single-arm, open-label, three-period, one fixed sequence crossover study). 1346.39.
c31477880	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia. 1346.9.
n00237515	Excretion in urine, faeces and bile and pharmacokinetics of radioactivity in plasma after oral and intravenous administration of [14C]BI 425809 to rats. A083/14JS.
n00277070	BI 425809 metabolite profiling and tentative metabolite identification in human 1346-0016. 29 September 2021.
n00243611	Absorption, disposition and excretion of [14C]BI 425809 in male and female minipigs. BI 425809. 07-Jul-2015

10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type = (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type = (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts ____	Yes ☐ No ☐ Total # of Attempts ____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ____	Yes ☐ No ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ____	Yes ☐ No ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.2 LISTING RESTRICTED CONCOMITANT MEDICATION

10.2.1 Strong CYP3A4 inhibitors

- boceprevir
- ceritinib
- clarithromycin
- cobicistat
- conivaptan
- diltiazem
- idelalisib
- indinavir
- itraconazole
- ketoconazole oral administration
- LCL161
- mifepristone
- mibefradil
- nefazodone
- nelfinafir
- posaconazole
- ribociclib
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- troleandomycin
- VIEKIRA PAK2
- voriconazole

10.2.2 Combinations of CYP 3A4 inhibitors

- danoprevir/ritonavir
- elvitegravir/ritonavir
- indinavir/ritonavir
- lopinavir/ritonavir
- paritaprevir/ritonavir/ombitasvir/dasbuvir
- saquinavir/ritonavir
- tipranavir/ritonavir

10.3 CKD-EPI FORMULA

eGFR (mL/min/1.73m^2) = $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$
$\times 1.018$ [if female] $\times 1.159$ [if Black]

SCr (standardized serum creatinine) = mg/dL

$\kappa = 0.7$ (females) or 0.9 (males)

$\alpha = -0.329$ (females) or -0.411 (males)

min = indicates the minimum of SCr/κ or 1

max = indicates the maximum of SCr/κ or 1

age = years

See references [R12-1392, R13-4387].

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

Document Number: c40079435 **Technical Version Number:1.0**

Document Name: clincial-trial-protocol-version-01

Title: Pharmacokinetics, safety and tolerability of BI 425809 (iclepertin) following oral administration in male and female participants with different degrees of renal impairment (severe, moderate and mild) compared with matched male and female participants with normal renal function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	23 Nov 2022 14:26 CET
Verification-Paper Signature Completion		23 Nov 2022 15:16 CET
Approval-Clinical Program [redacted]		23 Nov 2022 23:42 CET
Author-Trial Statistician		24 Nov 2022 08:11 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed