Clinical trial results:
A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of BI 425809 once daily with adjunctive Computerized Cognitive Training over 12 week treatment period in patients with schizophrenia

Summary

EudraCT number	2018-002740-82
Trial protocol	GB
Global end of trial date	04 November 2022

Results information

Result version number	v1 (current)
This version publication date	15 November 2023
First version publication date	15 November 2023

Trial information

Trial identification

Sponsor protocol code	1346-0038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03859973
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2022
Global end of trial reached?	Yes
Global end of trial date	04 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to provide proof of concept (PoC) data to assess the effect oncognition of oral once daily administration of iclepertin given for 12 weeks in patients with schizophrenia on stable antipsychotic treatment and adjunctive Computerised Cognitive Training (CCT). Other objectives of this trial were to explore endpoints to assess functioning and well-being of patients with schizophrenia and to evaluate safety and pharmacokinetics (PK) of iclepertin.

Protection of trial subjects:

An individual patient was to be withdrawn from trial treatment if:
- The patient wanted to withdraw from trial treatment or trial participation, without the need to justify the decision
- The patient needed to take concomitant drugs that interfered with the investigational product or were restricted
- The patient could no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy)
o If a patient became pregnant during the trial, the trial medication was to be stopped, the patient was to be discontinued from the trial and the patient was to be followed up until birth or otherwise termination of the pregnancy
o For further information, including the process for follow-up on the outcome of the pregnancy
- The patient had repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, was not willing or able to stick to the trial requirements in the future
- The patient exhibited suicidality, in the clinical judgement of the investigator or according to criteria below:
o Any suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
o Any suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity Rating Scale (C-SSRS) (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)
- Hb level <100 g/L (10 g/dL) AND absolute drop of >20 g/L (2 g/dL) since baseline (Visit 2); or
- The patient developed anaemia with symptoms of anaemia such as dizziness, fatigue, pallor, shortness of breath, etc. as determined by the investigator
- The patient needed to stop all current antipsychotic medications
- The patient’s disease state dramatically worsened, in clinical judgement of investigator
- The patient experienced severe or serious symptomatic infection with SARS-CoV-2

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 317
Worldwide total number of subjects	406
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	406
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in the trial once informed consent had been signed. Patients underwent computerised cognitive training (CCT) run-in for 2 weeks during the screening period. Patients compliant with the CCT run-in procedure and suitable after screening were randomised to the 12-week treatment period assigned at a ratio of 1:1 to 1 of 2 arms.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 425809 10 mg + Computerized Cognitive Training

Arm description:

Patients administered once daily (in the morning) two tablets of 5 milligram (mg) of BI 425809 (total BI 425809 dose= 10 mg) orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).

Arm type	Experimental
Investigational medicinal product name	BI 425809
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients administered once daily (in the morning) two tablets of 5 milligram (mg) of BI 425809 (total BI 425809 dose= 10 mg) orally for 12 weeks.

Arm title	Placebo + Computerized Cognitive Training

Arm description:

Patients administered once daily (in the morning) two tablets of Placebo matching BI 425809 5 milligram (mg) orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).

Arm type	Placebo
Investigational medicinal product name	Placebo matching BI 425809 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients administered once daily (in the morning) two tablets of Placebo matching BI 425809 5

milligram (mg) orally for 12 weeks.

Number of subjects in period 1[1]	BI 425809 10 mg + Computerized Cognitive Training	Placebo + Computerized Cognitive Training
Started	99	101
Completed	79	75
Not completed	20	26
Consent withdrawn by subject	8	9
Adverse event, non-fatal	3	5
Other reason than listed	3	2
COVID−19 related, not due to AE	3	4
Lost to follow-up	2	3
Protocol deviation	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 406 screened participants only 200 were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	BI 425809 10 mg + Computerized Cognitive Training
Reporting group description:	
Patients administered once daily (in the morning) two tablets of 5 milligram (mg) of BI 425809 (total BI 425809 dose= 10 mg) orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).	
Reporting group title	Placebo + Computerized Cognitive Training
Reporting group description:	
Patients administered once daily (in the morning) two tablets of Placebo matching BI 425809 5 milligram (mg) orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).	

Reporting group values	BI 425809 10 mg + Computerized Cognitive Training	Placebo + Computerized Cognitive Training	Total
Number of subjects	99	101	200
Age categorical			
Treated Set (TS) includes all patients in RS who were treated with at least 1 dose of the trial regimen (including both trial drug and CCT).			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	99	101	200
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Treated Set (TS) includes all patients in RS who were treated with at least 1 dose of the trial regimen (including both trial drug and CCT).			
Units: years			
arithmetic mean	37.9	38.5	
standard deviation	± 8.1	± 7.7	-
Sex: Female, Male			
Treated Set (TS) includes all patients in RS who were treated with at least 1 dose of the trial regimen (including both trial drug and CCT).			
Units: Participants			
Female	34	30	64
Male	65	71	136
Ethnicity (NIH/OMB)			
Treated Set (TS) includes all patients in RS who were treated with at least 1 dose of the trial regimen (including both trial drug and CCT).			
Units: Subjects			
Hispanic or Latino	12	16	28
Not Hispanic or Latino	87	85	172
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			

Treated Set (TS) includes all patients in RS who were treated with at least 1 dose of the trial regimen (including both trial drug and CCT).			
Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	4	5	9
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	44	40	84
White	47	51	98
More than one race	2	2	4
Unknown or Not Reported	2	0	2
Baseline MCCB neurocognitive composite T−score			
Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) neurocognitive composite T-score assesses 6 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving. MCCB neurocognitive T-scores in the general population have a mean of 50 and standard deviation of 10. A higher T-score indicates better cognition. Treated Set (TS). For one patient in the treated set MCCB neurocognitive T-Score at baseline was not measured.			
Units: T-score			
arithmetic mean	33.5	34.0	
standard deviation	± 12.0	± 11.3	-

End points

End points reporting groups

Reporting group title	BI 425809 10 mg + Computerized Cognitive Training

Reporting group description:

Patients administered once daily (in the morning) two tablets of 5 milligram (mg) of BI 425809 (total BI 425809 dose= 10 mg) orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).

Reporting group title	Placebo + Computerized Cognitive Training

Reporting group description:

Patients administered once daily (in the morning) two tablets of Placebo matching BI 425809 5 milligram (mg) orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).

Primary: Change from baseline in neurocognitive function as measured by the neurocognitive composite score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 12 weeks of treatment

End point title	Change from baseline in neurocognitive function as measured by the neurocognitive composite score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 12 weeks of treatment

End point description:

MCCB neurocognitive composite T-score assesses 6 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving. MCCB neurocognitive T-scores in the general population have a mean of 50 and standard deviation of 10. A higher T-score indicates better cognition. Change from baseline in MCCB neurocognitive composite T-score at Week 12 was modelled based on a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) which included the following fixed effects: categorical factor of planned treatment, visit (screening, baseline, week 6 and Week 12), planned treatment by visit interaction, continuous covariate of baseline value, baseline by visit interaction, categorical factor of age group, and continuous covariate of change from screening to baseline value. The Least Squares Mean (95 % Confidence Interval) at Week 12 is reported.
Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

At screening (28 days prior to first drug drug administration), at baseline and at Weeks 6 and 12 after first drug administration.

End point values	BI 425809 10 mg + Computerized Cognitive Training	Placebo + Computerized Cognitive Training		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	86		
Units: T-score				
least squares mean (confidence interval 95%)	1.580 (0.370 to 2.790)	2.466 (1.246 to 3.686)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) which included the following fixed effects: categorical factor of planned treatment, visit (screening, baseline, week 6 and Week 12), planned treatment by visit interaction, continuous covariate of baseline value, baseline by visit interaction, categorical factor of age group, and continuous covariate of change from screening to baseline value.

Comparison groups	BI 425809 10 mg + Computerized Cognitive Training v Placebo + Computerized Cognitive Training
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.3101
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.866
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.605
upper limit	0.833

Notes:

[1] - Point estimate=Least Square Mean of (BI 425809 10 mg + Computerized Cognitive Training) - Least Square Mean of (Placebo + Computerized Cognitive Training)

Secondary: Change from baseline in cognitive function as measured by the overall MCCB composite T score (including social cognition) after 12 weeks of treatment

End point title	Change from baseline in cognitive function as measured by the overall MCCB composite T score (including social cognition) after 12 weeks of treatment

End point description:

MCCB cognitive score comprises 10 tests, which assess 7 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. MCCB cognitive T-scores in the general population have a mean of 50 and standard deviation of 10. A higher T-score indicates better cognition. Change from baseline in MCCB overall composite T-score was modelled using a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) which included the following fixed effects: categorical factor of planned treatment, visit (screening, baseline, week 6 and Week 12), planned treatment by visit interaction, continuous covariate of baseline value, baseline by visit interaction, categorical factor of age group, and continuous covariate of change from screening to baseline value. The Least Squares Mean (95 % Confidence Interval) at Week 12 is reported.

End point type	Secondary

End point timeframe:

At screening (28 days prior to first drug drug administration), at baseline and at Weeks 6 and 12 after first drug administration.

End point values	BI 425809 10 mg + Computerized Cognitive Training	Placebo + Computerized Cognitive Training		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[2]	86[3]		
Units: T-score				
least squares mean (confidence interval 95%)	1.184 (-0.031 to 2.398)	2.235 (1.011 to 3.459)		

Notes:

[2] - Full Analysis Set (FAS).

[3] - Full Analysis Set (FAS).

Statistical analyses

Statistical analysis title	Statistican analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) which included the following fixed effects: categorical factor of planned treatment, visit (screening, baseline, week 6 and Week 12), planned treatment by visit interaction, continuous covariate of baseline value, baseline by visit interaction, categorical factor of age group, and continuous covariate of change from screening to baseline value.

Comparison groups	BI 425809 10 mg + Computerized Cognitive Training v Placebo + Computerized Cognitive Training
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2309 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.778
upper limit	0.676

Notes:

[4] - Point estimate= Least Square Mean of (BI 425809 10 mg + Computerized Cognitive Training) - Least Square Mean of (Placebo + Computerized Cognitive Training)

Secondary: Change from baseline in the effect of cognitive deficit on day-to-day functioning as measured by SCoRS total score after 12 weeks of treatment

End point title	Change from baseline in the effect of cognitive deficit on day-to-day functioning as measured by SCoRS total score after 12 weeks of treatment

End point description:

Schizophrenia Cognition Rating Scale (SCoRS) is a 20-item interview-based assessment of cognitive deficits and the degree to which they affect day-to-day functioning. Each item is rated on a 4-point scale. SCoRS total score is between 20 and 80 where higher score values represent greater degree of impairment in day-to-day functions due to cognitive deficits. The composite score was the average of non-missing responses. If five or more of the 20 items were missing, the composite score was missing for that participant at the visit.
Change from baseline in SCoRS total score after 12 weeks of treatment was modelled using an Analysis of Covariance (ANCOVA) which included the following fixed effects: categorical factor of planned treatment, continuous covariate of baseline value, categorical factor of age group.
FAS includes all patients in treated set (TS) who had non-missing baseline and at least 1 non-missing post-baseline on-treatment measurement of the primary efficacy endpoint.

End point type	Secondary

End point timeframe:

At baseline and at 12 weeks after first drug administration.

End point values	BI 425809 10 mg + Computerized Cognitive Training	Placebo + Computerized Cognitive Training		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82[5]	75[6]		
Units: units on a scale				
least squares mean (confidence interval 95%)	-2.495 (-3.724 to -1.266)	-3.072 (-4.358 to -1.787)		

Notes:

[5] - Only patients with non-missing results at Week 12 are reported.

[6] - Only patients with non-missing results at Week 12 are reported.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis of Covariance (ANCOVA) which included the following fixed effects: categorical factor of planned treatment, continuous covariate of baseline value, categorical factor of age group.

Comparison groups	BI 425809 10 mg + Computerized Cognitive Training v Placebo + Computerized Cognitive Training
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.5237
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.577
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.207
upper limit	2.362

Notes:

[7] - Point estimate= Least Square Mean of (BI 425809 10 mg + Computerized Cognitive Training) - Least Square Mean of (Placebo + Computerized Cognitive Training)

Secondary: Change from baseline in Positive and Negative Syndrome Scale (PANSS) total score after 12 weeks of treatment

End point title	Change from baseline in Positive and Negative Syndrome Scale (PANSS) total score after 12 weeks of treatment

End point description:

PANSS was used to evaluate broad psychopathology associated with schizophrenia disease state. The PANSS has 30 items. Each is rated from 1 to 7 points. The total factor score is the summation of the actual points for each item, leading the total score ranging from 30 to 210; a higher score indicates a worse disease condition.
Change from baseline in PANNS total score after 12 weeks of treatment was modelled based on a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) which included the following fixed effects: categorical factor of planned treatment, visit (baseline, Week 6 and Week 12), planned treatment by visit interaction, continuous

covariate of baseline value, baseline by visit interaction, categorical factor of age group. The Least Squares Mean (95 % Confidence Interval) at Week 12 is reported.
Full Analysis Set (FAS).

End point type	Secondary

End point timeframe:

At baseline and at Weeks 6 and 12 after first drug administration.

End point values	BI 425809 10 mg + Computerized Cognitive Training	Placebo + Computerized Cognitive Training		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	85[8]		
Units: units on a scale				
least squares mean (confidence interval 95%)	-2.749 (-4.732 to -0.765)	-2.080 (-4.104 to -0.055)		

Notes:

[8] - One patient in the FAS was excluded due to lack of post-baseline PANSS total score values.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) which included the following fixed effects: categorical factor of planned treatment, visit (baseline, Week 6 and Week 12), planned treatment by visit interaction, continuous covariate of baseline value, baseline by visit interaction, categorical factor of age group.

Comparison groups	BI 425809 10 mg + Computerized Cognitive Training v Placebo + Computerized Cognitive Training
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.642
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.669
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	2.172

Notes:

[9] - Point estimate= Least Square Mean of (BI 425809 10 mg + Computerized Cognitive Training) - Least Square Mean of (Placebo + Computerized Cognitive Training)

Secondary: Percentage of patients with any Adverse Event (AE) and with serious adverse events (SAEs)

End point title	Percentage of patients with any Adverse Event (AE) and with serious adverse events (SAEs)

End point description:

Percentage of patients with any Adverse Event (AE) and with serious adverse events (SAEs) is reported. Percentages were rounded to one decimal place.

Treated Set (TS) includes all patients in randomized set (RS) who were treated with at least 1 dose of the trial regimen (including both trial drug and computerized cognitive training (CCT)).

End point type	Secondary

End point timeframe:

From first dose of study drug administration until four weeks after the last dose of study drug administration, up to 16 weeks.

End point values	BI 425809 10 mg + Computerized Cognitive Training	Placebo + Computerized Cognitive Training		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	101		
Units: percentage of participants				
number (not applicable)				
Any adverse event	39.4	56.4		
Serious adverse events	1.0	2.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug administration until four weeks after the last dose of study drug administration, up to 16 weeks.

Adverse event reporting additional description:

Treated Set (TS) includes all patients in randomized set (RS) who were treated with at least 1 dose of the trial regimen (including both trial drug and computerized cognitive training (CCT)).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo + Computerized Cognitive Training

Reporting group description:

Patients administered once daily (in the morning) two tablets of 5 milligram (mg) of Placebo matching BI 425809 orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).

Reporting group title	BI 425809 10 mg + Computerized Cognitive Training

Reporting group description:

Patients administered once daily (in the morning) orally two tablets of 5 milligram (mg) of BI 425809 (total BI 425809 dose= 10 mg) orally for 12 weeks. Concomitantly patients received non-pharmacological adjunctive computerized cognitive training (CCT).

Serious adverse events	Placebo + Computerized Cognitive Training	BI 425809 10 mg + Computerized Cognitive Training	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 101 (1.98%)	1 / 99 (1.01%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Delirium			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo + Computerized Cognitive Training	BI 425809 10 mg + Computerized Cognitive Training	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 101 (15.84%)	9 / 99 (9.09%)	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 101 (10.89%)	7 / 99 (7.07%)	
occurrences (all)	14	9	
Gastrointestinal disorders			

Vomiting subjects affected / exposed occurrences (all)	6 / 101 (5.94%) 7	3 / 99 (3.03%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2018	Global Amendment 1, dated 21 Dec 2018 (prior to enrolment of the first patient; Independent Ethics Committee/Institutional review board (IEC/IRB) approval required): Proof of clinical concept (PoCC) was changed to proof of concept (PoC) to reflect exploratory nature of the trial. Exclusion criterion no. 24 was amended to remove exception for benzodiazepines (they were not included in the urine drug screen. New exclusion criterion no. 28 was added to exclude patients with an allergy to BI 425809 (iclepertin) and/or any of the excipients (including lactose) or placebo ingredients.
02 October 2019	Global Amendment 2, dated 02 Oct 2019 (IEC/IRB approval required): The following measures were introduced to minimise CCT exposure prior to randomisation: 1) Assessment of laboratory results was ideally done prior to start of CCT run-in; 2) CCT run-in was to be stopped once compliance was established; 3) CCT run-in was not to be repeated for re-screened patients. Screening Period was allowed to be extended up to 10 days (for total 38 days) in case cannabis re-testing per exclusion criterion 24 was performed, and time frame for cannabis re-testing was removed from Exclusion Criterion 24. Exclusion Criterion 19 was amended to exclude patients with known history of human immunodeficiency virus (HIV) infection based on review of medical history. The need for CCT sessions to be minimum 10 consecutive minutes in order to be included in weekly accrual time was removed. Sites were to determine the reason if the number of doses taken was greater than 100%. The MATRICS Consensus Cognitive Battery (MCCB) assessments at Visit 4 and(e)EoT Visit had to be started at the same time of the day as at Visit 2 (+/- 60
21 July 2020	Global Amendment 3, dated 21 Jul 2020 (IEC/IRB approval required): Schizophrenia Cognition Rating Scale (SCoRS) assessment was added to Visit 1 (Screening). Additional follow up for patients with hemoglobin (Hb) decrease >20 g/L (2 g/dL) since baseline (Visit 2) or leading to symptoms of anaemia (e.g. dyspnoea, dizziness, etc.). The following inclusion criteria were re-phrased: 1) Criterion 4 to remove specific psychotropic medications and refer to them as examples; 2) Criterion 6 to allow randomisation of patients who did not meet the CCT run-in compliance threshold pending a documented discussion between the investigator and the Clinical Trial Manager (CTM) or Clinical Trial Lead(CTL); 3) Criterion 7 to remove the requirement to comply with at-home CCT exercises (to avoid overlap with Criterion 6). The following changes were made to address the COVID-19 pandemic: 1) New exclusion criterion 29 for patients with known active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within the last 30 days prior to randomisation; 2) Additional criterion for discontinuation of trial treatment for patients that experienced severe or serious symptomatic infection with SARS-CoV-2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	Patient involvement in the trial began in June 2019 and completed in November 2022, which included the period during which the COVID-19 pandemic was occurring globally. The trial was at the stage of recruitment when the pandemic occurred. Enrolment, randomisation, and site initiations for the trial were put on hold at all sites in March 2020 and re-started at different times in different countries depending on the local situation.	-

Notes:

Limitations and caveats

None reported