



Clinical trial results:

A phase III randomized, double-blind, placebo-controlled, parallel group trial to examine the efficacy and safety of Iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-2)

Summary

EudraCT number	2020-003744-84
Trial protocol	HU PL NL FR SK ES HR RO
Global end of trial date	17 November 2024

Results information

Result version number	v1 (current)
This version publication date	30 November 2025
First version publication date	30 November 2025

Trial information

Trial identification

Sponsor protocol code	1346-0012
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04846881
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	18 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2024
Global end of trial reached?	Yes
Global end of trial date	17 November 2024
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 assess the efficacy in improving cognitive impairment using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) in patients with schizophrenia treated for 26 weeks with iclepertin 10 mg as compared with placebo.

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

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

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required. Each participant and their study partner signed and received a copy of their informed consent and were informed that they were free to withdraw consent at any time without penalty or prejudice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 102
Country: Number of subjects enrolled	Brazil: 133
Country: Number of subjects enrolled	Chile: 26
Country: Number of subjects enrolled	Croatia: 35
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Japan: 97
Country: Number of subjects enrolled	Malaysia: 45
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Romania: 11

Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	United States: 193
Worldwide total number of subjects	840
EEA total number of subjects	195

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)	840
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised, placebo-controlled, double-blind, multi-centre, multi-national, 26-week, parallel group trial, with a 4-week safety follow-up period. Participants had to complete the treatment and follow-up periods before they could enter the open label extension study.

Pre-assignment

Screening details:

Participants were screened for eligibility which ensured that they met all inclusion and none of the exclusion criteria. Participants were not allocated to a treatment sequence if any of the entry criteria were violated. One subject was randomised in error and excluded from the treated set.

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, Carer, Data analyst, Assessor, Monitor

Blinding implementation details:

Except for the independent data monitoring committee (DMC), the patients, investigators, central reviewers, and everyone involved in conduct of the trial or analysis or with any other interest in this double-blind trial remained blinded with regards to the randomised treatment assignments until the database was declared ready for analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iclepertin 10 mg

Arm description:

This arm comprised participants who received 10 mg tablet of iclerpertin orally once daily, with doses administered at least 24 hours (hrs) apart, taken with water. Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

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

Dosage and administration details:

One tablet of 10 mg icleperptin taken once daily for 26 weeks

Arm title	Placebo
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Arm description:

This arm comprised participants who received 10 mg tablet of iclerpertin-matched Placebo orally once daily, with doses administered at least 24 hrs apart, taken with water. Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

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

Dosage and administration details:

One tablet of matching placebo taken once daily for 26 weeks

Number of subjects in period 1^[1]	Iclepertin 10 mg	Placebo
Started	305	305
Treated	305	305
Completed	267	267
Not completed	38	38
Adverse event, non-fatal	14	15
Technical problems	-	1
Perceived lack of efficacy	5	2
Protocol deviation	6	4
No reason available	1	3
Burden of study procedures	7	3
Change of residence	2	-
Other than listed	3	10

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: The worldwide number enrolled includes subjects who were excluded for several reasons and were ineligible to participate in the study. Only patients who met all inclusion and none of the exclusion criteria were randomised to study treatment.

Baseline characteristics

Reporting groups

Reporting group title	Iclepertin 10 mg
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Reporting group description:

This arm comprised participants who received 10 mg tablet of iclerpertin orally once daily, with doses administered at least 24 hours (hrs) apart, taken with water. Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

Reporting group title	Placebo
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Reporting group description:

This arm comprised participants who received 10 mg tablet of iclerpertin-matched Placebo orally once daily, with doses administered at least 24 hrs apart, taken with water. Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

Reporting group values	Iclepertin 10 mg	Placebo	Total
Number of subjects	305	305	610
Age categorical			
Randomized Set (RS): included all patients who signed informed consent and were randomized into the trial, regardless of whether a patient was treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS. Patients in the RS were analyzed under the randomized trial medication.			
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)	305	305	610
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Randomized Set (RS): included all patients who signed informed consent and were randomized into the trial, regardless of whether a patient was treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS. Patients in the RS were analyzed under the randomized trial medication.			
Units: years			
arithmetic mean	36.6	35.5	
standard deviation	± 8.5	± 8.5	-
Sex: Female, Male			
Randomized Set (RS): included all patients who signed informed consent and were randomized into the trial, regardless of whether a patient was treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS. Patients in the RS were analyzed under the randomized trial medication.			
Units: Subjects			
Male	204	212	416
Female	101	93	194
Ethnicity (NIH/OMB)			
Randomized Set (RS): included all patients who signed informed consent and were randomized into the trial, regardless of whether a patient was treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS. Patients in the RS were analyzed under the randomized trial medication.			

Units: Subjects			
Hispanic or Latino	89	78	167
Not Hispanic or Latino	199	213	412
Unknown or Not Reported	17	14	31
Race (NIH/OMB)			
Randomized Set (RS): included all patients who signed informed consent and were randomized into the trial, regardless of whether a patient was treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS. Patients in the RS were analyzed under the randomized trial medication.			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	76	69	145
Native Hawaiian or Other Pacific Islander	3	1	4
Black or African American	41	44	85
White	166	172	338
More than one race	1	4	5
Unknown or Not Reported	17	14	31

End points

End points reporting groups

Reporting group title	Iclepertin 10 mg
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Reporting group description:

This arm comprised participants who received 10 mg tablet of iclerpertin orally once daily, with doses administered at least 24 hours (hrs) apart, taken with water. Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

Reporting group title	Placebo
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Reporting group description:

This arm comprised participants who received 10 mg tablet of iclerpertin-matched Placebo orally once daily, with doses administered at least 24 hrs apart, taken with water. Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

Subject analysis set title	Iclepertin 10 mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

This arm comprised participants who received 10 mg tablet of iclerpertin orally once daily, with doses administered at least 24 hours (hrs) apart, taken with water. Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

Subject analysis set title	Placebo
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Subject analysis set type	Per protocol
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Subject analysis set description:

This arm comprised participants who received 10 mg tablet of iclerpertin-matched Placebo orally once daily, with doses administered at least 24 hrs apart, taken with water.

Participants were treated for 26 weeks, followed by 4 weeks follow-up after trial drug termination.

Primary: Change from baseline in the overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 26 weeks of treatment

End point title	Change from baseline in the overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 26 weeks of treatment
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End point description:

The change from baseline in MCCB (MATRICS Consensus Cognitive Battery) overall composite T-score at Week 26 is reported. This was analyzed using a mixed-effects model for repeated measurements (MMRM) comparing the change from baseline in MCCB overall composite T-score at Week 26 between iclerpertin 10 mg daily and placebo. The MCCB comprises 10 tests to measure cognitive performance in 7 cognitive domains: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The composite T-score is derived from the 7 cognitive domain T-scores. The T-score is standardized to the normative population with a mean of 50 and standard deviation of 10. A higher MCCB overall composite T-score indicates better cognition. The Randomized Set (RS) included all patients with consent, excluding those randomized in error who stopped before treatment. Patients were analyzed by their assigned medication.

End point type	Primary
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End point timeframe:

The MMRM model is a longitudinal analysis which incorporated values at screening, baseline and at Week 12 and Week 26. The data presented here represent the Least Squares Mean at Week 26.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	305		
Units: T-score				
least squares mean (standard error)	2.719 ($\pm$ 0.3377)	1.997 ($\pm$ 0.3345)		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

The model included fixed categorical effects of treatment at each visit and the stratification factor (screening MCCB overall composite T-score) and fixed effects for the continuous covariate of baseline at each visit. Visit was treated as a repeated measure with unstructured covariance structure for within-participant dependencies. The primary comparison was iclepertin 10 mg daily vs. placebo at Week 26.

Comparison groups	Iclepertin 10 mg v Placebo
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1291
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.722
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.211
upper limit	1.656
Variability estimate	Standard error of the mean
Dispersion value	0.4753

Secondary: Change from baseline in SCoRS (Schizophrenia Cognition Rating Scale) interviewer total score at Week 26

End point title	Change from baseline in SCoRS (Schizophrenia Cognition Rating Scale) interviewer total score at Week 26
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End point description:

Change from baseline in SCoRS (Schizophrenia Cognition Rating Scale) interviewer total score at Week 26, using an MMRM model, is reported. SCoRS analyzed functional capacity through 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, with higher ratings reflecting a greater degree of impairment. The Randomized Set (RS) included all patients with consent, excluding those randomized in error who stopped before treatment. Patients were analyzed by their assigned medication.

End point type	Secondary
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End point timeframe:

The MMRM model is a longitudinal analysis which incorporated values at screening, baseline and at Week 12 and Week 26. The data presented here represent the Least Squares Mean at Week 26.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	305		
Units: Scores on a scale				
least squares mean (standard error)	-5.053 ($\pm$ 0.4268)	-5.767 ($\pm$ 0.4261)		

Statistical analyses

Statistical analysis title	Analysis 2
Statistical analysis description:	
The model included the discrete fixed effects of treatment at each visit, fixed categorical covariate of the stratification factor using the screening MCCB overall composite T-score, and continuous fixed effects for the corresponding baseline endpoint value at each visit. Visit was treated as the repeated measure with an unstructured covariance structure to model the within-subject measurements. Subjects were considered as a random effect.	
Comparison groups	Iclepertin 10 mg v Placebo
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2375
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.714
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.472
upper limit	1.901
Variability estimate	Standard error of the mean
Dispersion value	0.6042

Secondary: Change from baseline in VRFCAT (Virtual Reality Functional Capacity Assessment Tool) adjusted total time T-score at Week 26

End point title	Change from baseline in VRFCAT (Virtual Reality Functional Capacity Assessment Tool) adjusted total time T-score at Week 26
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End point description:

Change from baseline in VRFCAT (Virtual Reality Functional Capacity Assessment Tool) adjusted total time T-score at Week 26, using an MMRM model, is reported. The VRFCAT is a virtual reality shopping trip performed on a tablet. The task has several linked and sequential scenarios, including matching a recipe to the content of kitchen cabinets, preparing a shopping list, taking the correct bus, shopping efficiently, and catching the correct return bus. These tasks are performed in a fixed sequence. The summary measures from the VRFCAT assessment included adjusted total time, number of errors, number of forced progressions and their associated T-scores. The key secondary endpoint is the adjusted total time T-score.

The Randomized Set (RS) included all patients with consent, excluding those randomized in error who

stopped before treatment. Patients were analyzed by their assigned medication.

End point type	Secondary
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End point timeframe:

The MMRM model is a longitudinal analysis which incorporated values at screening, baseline and at Week 12 and Week 26. The data presented here represent the Least Squares Mean at Week 26.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	305		
Units: T-score				
least squares mean (standard error)	3.898 ($\pm$ 0.7531)	3.565 ($\pm$ 0.7481)		

Statistical analyses

Statistical analysis title	Analysis 3
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Statistical analysis description:

The model included the discrete fixed effects of treatment at each visit, fixed categorical covariate of the stratification factor using the screening MCCB overall composite T-score, and continuous fixed effects for the corresponding baseline endpoint value at each visit. Visit was treated as the repeated measure with an unstructured covariance structure to model the within-subject measurements. Subjects were considered as a random effect.

Comparison groups	Iclepertin 10 mg v Placebo
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7541
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.333
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.753
upper limit	2.419
Variability estimate	Standard error of the mean
Dispersion value	1.062

Secondary: Change from screening Visit 1a to Week 24 in Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) total score

End point title	Change from screening Visit 1a to Week 24 in Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) total score
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End point description:

Change from screening Visit 1a to Week 24 in PRECIS total score, using an MMRM model, is reported. The PRECIS total score measures changes in patients' subjective cognitive impairment associated with

schizophrenia (CIAS) from Screening Visit 1a to Week 24. PRECIS is a 28-item patient-reported outcome assessing CIAS over the past week across 6 domains: Memory (6 items), Communication (4), Self-Control (3), Executive Function (4), Attention (6), and Sharp Thinking (3). Two additional items assess overall bother. Responses use a 5-point Likert scale (1=not at all, 5=very hard), with higher scores indicating worse experiences. The Total Score is the average of the first 26 items. The questionnaire takes 5-15 minutes to complete and provides insights into CIAS impact. The Randomized Set (RS) included all patients with consent, excluding those randomized in error who stopped before treatment. Patients were analyzed by their assigned medication.

End point type	Secondary
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End point timeframe:

The MMRM model is a longitudinal analysis which incorporated values at screening, and at Week 15 and Week 24. The data presented here represent the Least Squares Mean at Week 24.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	305		
Units: Scores on a scale				
least squares mean (standard error)	-0.333 ($\pm$ 0.0312)	-0.345 ($\pm$ 0.031)		

Statistical analyses

Statistical analysis title	Analysis 4
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Statistical analysis description:

The model included the discrete fixed effects of treatment at each visit, fixed categorical covariate of the stratification factor using the screening MCCB overall composite T-score, and continuous fixed effects for the corresponding baseline endpoint value at each visit. Visit was treated as the repeated measure with an unstructured covariance structure to model the within-subject measurements. Subjects were considered as a random effect.

Comparison groups	Iclepertin 10 mg v Placebo
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7769
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.099
Variability estimate	Standard error of the mean
Dispersion value	0.044

Secondary: Change from baseline in the T-score of the number of correct responses on Tower of London (ToL) at Week 26

End point title	Change from baseline in the T-score of the number of correct responses on Tower of London (ToL) at Week 26
End point description:	
Change from baseline in the T-score of the number of correct responses on Tower of London at Week 26, using an analysis of covariance (ANCOVA) model, is reported. The Tower of London is a neurophysiological test used to assess executive functions such as reasoning and problem-solving ability. In this test, participants in the RS were shown two images presented on opposite sides of a tablet screen. Each image showed a different configuration of 3 colored balls arranged on 3 pegs. The patient was required to accurately determine the total number of times the balls in one picture would have to be moved in order to make the arrangement of balls identical to that of the other opposing picture, while employing the standard rules applicable in tower tests (balls are moved one at a time and balls on top of other balls must be moved first). Eight alternative forms were available, and the outcome measure was the number of correct responses. The administration time was about 7 minutes.	
End point type	Secondary
End point timeframe:	
Baseline and at Week 26	

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	305		
Units: T-Score				
least squares mean (standard error)	0.148 ($\pm$ 0.6446)	1.283 ($\pm$ 0.6433)		

Statistical analyses

Statistical analysis title	Analysis 5
Statistical analysis description:	
For change from baseline to Week 26 in the T-score of the number of correct responses on ToL, an analysis of covariance (ANCOVA) model including treatment, stratification factor of screening MCCB overall composite T-score (<30, $\geq$ 30), and baseline number of correct responses on ToL T-score were fitted to the data.	
Comparison groups	Iclepertin 10 mg v Placebo
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2133
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.925
upper limit	0.654
Variability estimate	Standard error of the mean
Dispersion value	0.911

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious AEs and other AEs: From first dose of study drug to last dose over a 26-week treatment period, plus a 12-day residual effect period.

All-cause mortality: From first drug administration till end of study over a 30-week observation period.

Adverse event reporting additional description:

The Treated Set (TS) included all patients who signed informed consent and were treated with at least one dose of the trial medication. Patients in the TS were analyzed under the actual trial medication received at randomization.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Iclepertin 10 mg
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Reporting group description: -

Serious adverse events	Placebo	Iclepertin 10 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 305 (5.25%)	11 / 305 (3.61%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurofibroma			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniofacial fracture			
subjects affected / exposed	2 / 305 (0.66%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumocephalus			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	0 / 305 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 305 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subarachnoid haemorrhage			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 305 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal fistula			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 305 (0.00%)	1 / 305 (0.33%)	
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			
Pulmonary embolism			
subjects affected / exposed	0 / 305 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	5 / 305 (1.64%)	4 / 305 (1.31%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	4 / 305 (1.31%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	2 / 305 (0.66%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 305 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	0 / 305 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis bacterial			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathogen resistance			
subjects affected / exposed	1 / 305 (0.33%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 305 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Iclepertin 10 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 305 (19.34%)	73 / 305 (23.93%)	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 305 (8.20%)	30 / 305 (9.84%)	
occurrences (all)	34	37	
Somnolence			
subjects affected / exposed	15 / 305 (4.92%)	18 / 305 (5.90%)	
occurrences (all)	30	36	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	15 / 305 (4.92%)	20 / 305 (6.56%)	
occurrences (all)	16	22	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 305 (5.57%)	22 / 305 (7.21%)	
occurrences (all)	20	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2022	BI 425809 was replaced by Icleptin in the title page and whole document; Clarification that the key secondary efficacy endpoint for the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) is the adjusted total time T-score in the synopsis and sections 2.1.3 and 7; Placebo Control Reminder Script (PCRS) was added to the flowchart and abbreviations; Footnote number changes for Mini International Neuropsychiatric Interview (MINI) and AiCure to 7 and 8 respectively; Addition of footnote #20 to clarify that study partner is required for Schizophrenia Cognition Rating Scale (SCoRS) and Positive and Negative Syndrome Scale (PANSS) interviews at least at Visit 2 and end of trial (EOT) in the flowchart endnotes; Change in the requirement for ophthalmologic assessments to be performed in case of moderate to severe vision related AEs in Sections 1.4.2 and 5.2.6.3; Clarification that Paxlovid should not be used concomitantly with the study drug in Sections 1.4.2 and 3.3.4.1. Patients who require treatment with Paxlovid should temporarily discontinue the study drug; Refinement of the Healthcare resource utilization (HCRU) further endpoint; Inclusion criteria #5 updated to permit patients who are on 2 anti-psychotics that at least one has to be within the approved label dose range and the other must not exceed the maximum daily dose per local label in Section 3.3.2; Inclusion criteria #6 updated – removed reference to hypnotic load up to 0.25 mg brotizolam equivalence. Clarified that other psychoactive medications cannot exceed the maximum daily dose per local label in Section 3.3.2; Exclusion criteria #2 updated to exclude patients with epilepsy in Section 3.3.3; Exclusion criteria #8 updated to exclude the use of esketamine as well as ketamine; Exclusion criteria #10 updated to exclude only those patients who have previously been treated with icleptin in Section 3.3.3;
27 October 2022	Exclusion criteria #11 updated including related footnote in Section 3.3.3; Exclusion criteria #18 updated to exclude patients who currently have anemia in Section 3.3.3; Exclusion criteria #26 (Section 3.3.3) updated to clarify that list of ingredients can be found in the Investigator's Brochure; Added guidance related to lost to follow-up patients and included a reference to retention guide in Section 3.3.4; Removal that patients need to be followed until EOT+28 days in Section 3.3.4.2; Addition of new reason for withdrawing (patients need to take restricted medications) in Section 3.3.4.2; Removal of quetiapine as an example for sedative medications in 4.2.2.1; Clarify that short term use of opioids for pain, cough or diarrhea during the treatment period was not allowed in 4.2.2.1; Addition of vaccination for COVID-19 in the permitted therapies in 4.2.2.1; Addition of reference to section 6.2.1 for Clinical Global Impressions – Severity (CGI-S), Updated number of items included in the Schizophrenia Caregiver Questionnaire (SCQ), and Addition of HCRU details that are collected in Section 5.1; Removal of number of items for AIMS in Section 5.2; Confirmation that re-test is permitted at visit 1a in case patients are drug screen positive at Visit 1 in 5.2.3; Addition of reference to section 3.3.4.2 in case patient becomes pregnant in 5.2.6.2.3;

27 October 2022	Confirm that patients must consent to the use of AiCure app. Use of AiCure was not a specific reason for discontinuation in Section 5.6.2; Confirmed that Verified Clinical Trials will be used only for countries that have not opted-out by local amendment in Section 5.6.3; Removal of examples of scales that should be done by the same rater in Section 6.2.1; Description added for CGI-S requirements in 6.2.1; Updated paragraph regarding patient and study partner informed consents in 6.2.2; Addition of reference to appendix 10.3 in Section 6.2.3; Update of the different scenarios in case of early discontinuation and clarify re-start trial medication in Section 6.2.3.4; Clarification that randomized set will exclude patients randomized by error and discontinued from the study before the start of trial medication in Section 7.2.1; Update of the statistical model in Section 10.2; Revision of wording to indicate that the caregiver will be asked to complete the additional questionnaires in 10.2; Addition of exceptional circumstances in addition to COVID-19 in Section 10.3; Clarification that study partner contacts and assessments can be also impacted in 10.3; Inclusion of analysis by the Central Lab in addition to blood sampling and inclusion of also secondary endpoints description in case of any exceptional circumstances in Section 10.3.
18 September 2023	Added footnote 21 to flowchart and footnotes: Columbia Suicidality Severity Rating Scale (C-SSRS) may be repeated based on investigator discretion; Corrected typo in drug name (BI 425908 was changed to Iclepertin) in Section 3.3; Clarification on calculation of compliance based on tablets removed from blisters in 4.3 Compliance; Reinforcement of documenting details for any positive suicidal ideation and to provide comments on the clinical significance and any additional follow-up action items. The C-SSRS may be repeated at an unscheduled visit based on investigator discretion (Section 5.2, Assessment of Safety); Added "preferably" within 30 minutes before dose to on treatment PK sampling timepoints, added "approximately" to other PK sampling timepoints. Added reminder that actual times are collected in the eCRF (Appendix 10.1).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported