



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-1)

Summary

EudraCT number	2020-003760-11
Trial protocol	DE SE PL NO IT
Global end of trial date	01 October 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	1346-0011
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04846868
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	08 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2024
Global end of trial reached?	Yes
Global end of trial date	01 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to assess the efficacy of iclepertin in improving cognitive impairment, daily functioning, and improve reasoning and problem solving in patients with schizophrenia.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 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	Australia: 1
Country: Number of subjects enrolled	Brazil: 90
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	China: 127
Country: Number of subjects enrolled	Colombia: 136
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Greece: 28
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 92
Country: Number of subjects enrolled	Mexico: 72
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Türkiye: 17
Country: Number of subjects enrolled	United States: 149
Worldwide total number of subjects	817
EEA total number of subjects	121

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)	817
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Randomized, placebo-controlled, double-blind, multicenter, multinational, 26-week, parallel group trial. Patients could roll-over to safety follow-up extension trial (1346-0014). A dedicated ocular sub-study was implemented in several countries participating in the trial to investigate the ocular safety of iclepertin in patients with schizophrenia.

Pre-assignment

Screening details:

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

Period 1

Period 1 title	Randomization period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

Patients, investigators, central reviewers, and everyone involved in the trial conduct or analysis or with any other interest remained blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iclepertin 10 mg

Arm description:

Patients with schizophrenia took orally once a day one 10 milligram (mg) tablet of iclepertin.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Placebo-matching Iclepertin 10 mg

Arm description:

Patients with schizophrenia took orally once a day one tablet of placebo-matching iclepertin.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg
Started	312	308
Completed	312	307
Not completed	0	1
Not treated	-	1

Period 2

Period 2 title	Treatment period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

Patients, investigators, central reviewers, and everyone involved in the trial conduct or analysis or with any other interest remained blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iclepertin 10 mg

Arm description:

Patients with schizophrenia took orally once a day one 10 milligram (mg) tablet of iclepertin.

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 10 milligram (mg) tablet once a day.

Arm title	Placebo-matching Iclepertin 10 mg
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Arm description:

Patients with schizophrenia took orally once a day one tablet of placebo-matching iclepertin.

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 once a day.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: From the 620 subjects randomized to a treatment, 1 did not receive treatment. The baseline period is reported on the randomized set, excluding the one subject that was not treated due to an error in randomization.

Number of subjects in period 2^[2]	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg
Started	312	307
Ocular safety sub-study	26 ^[3]	22 ^[4]
Completed	266	273
Not completed	46	34
Other reason listed	20	10
Adverse event, non-fatal	12	11
Perceived lack of efficacy	3	2
Protocol deviation	6	2

No reason available	2	5
Burden of study procedures	1	1
Change of residence	2	3

Notes:

[2] - 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: From the 817 subjects screened, 620 were randomized to a treatment.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 26 of the subjects were additionally participating in an ocular safety sub-study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 22 of the subjects were additionally participating in an ocular safety sub-study.

Baseline characteristics

Reporting groups

Reporting group title	Iclepertin 10 mg
Reporting group description:	
Patients with schizophrenia took orally once a day one 10 milligram (mg) tablet of iclepertin.	
Reporting group title	Placebo-matching Iclepertin 10 mg
Reporting group description:	
Patients with schizophrenia took orally once a day one tablet of placebo-matching iclepertin.	

Reporting group values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg	Total
Number of subjects	312	307	619
Age categorical			
Randomized set: all patients randomized into the trial, regardless of whether a patient was treated with trial medication. One patient was randomized in error and discontinued from the trial before the start of 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)	312	307	619
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Randomized set: all patients randomized into the trial, regardless of whether a patient was treated with trial medication. One patient was randomized in error and discontinued from the trial before the start of trial medication.			
Units: years			
arithmetic mean	34.5	33.8	
standard deviation	± 9.0	± 8.8	-
Sex: Female, Male			
Randomized set: all patients randomized into the trial, regardless of whether a patient was treated with trial medication. One patient was randomized in error and discontinued from the trial before the start of trial medication.			
Units: Participants			
Male	205	203	408
Female	107	104	211
Race (NIH/OMB)			
Randomized set: all patients randomized into the trial, regardless of whether a patient was treated with trial medication. One patient was randomized in error and discontinued from the trial before the start of trial medication.			
Units: Subjects			
American Indian or Alaska Native	53	63	116
Asian	88	97	185
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	21	19	40

White	139	122	261
More than one race	10	6	16
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomized set: all patients who signed informed consent and were randomized into the trial, regardless of whether a patient was treated with trial medication. One patient was excluded from the randomized set due to an error in randomization and discontinued from the trial before the start of trial medication.			
Units: Subjects			
Hispanic or Latino	123	123	246
Not Hispanic or Latino	189	184	373
Unknown or Not Reported	0	0	0
MATRICES Consensus Cognitive Battery (MCCB) overall composite T-score			
MCCB comprises 10 tests, which assess 7 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The larger the MCCB overall composite T-score, the better patient cognition. A mean T-score of 50 and a standard deviation of 10 reflects the T-score on a general population.			
Randomized set.			
Units: Units on a scale			
arithmetic mean	28.6	28.8	
standard deviation	± 13.7	± 14.0	-

End points

End points reporting groups

Reporting group title	Iclepertin 10 mg
Reporting group description: Patients with schizophrenia took orally once a day one 10 milligram (mg) tablet of iclepertin.	
Reporting group title	Placebo-matching Iclepertin 10 mg
Reporting group description: Patients with schizophrenia took orally once a day one tablet of placebo-matching iclepertin.	
Reporting group title	Iclepertin 10 mg
Reporting group description: Patients with schizophrenia took orally once a day one 10 milligram (mg) tablet of iclepertin.	
Reporting group title	Placebo-matching Iclepertin 10 mg
Reporting group description: Patients with schizophrenia took orally once a day one tablet of placebo-matching iclepertin.	
Subject analysis set title	Iclepertin 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Patients with schizophrenia who took orally once a day one 10 milligram (mg) tablet of iclepertin in the main part of the trial and participated in the ocular sub-study.	
Subject analysis set title	Placebo-matching Iclepertin 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Patients with schizophrenia who took orally once a day one tablet of placebo-matching iclepertin in the main part of the trial and participated in the ocular sub-study.	

Primary: Change from baseline in 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 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 to Week 26 in MCCB overall composite T-score. MCCB comprises 10 tests, assessing cognitive function. The larger the MCCB overall composite T-score, the better patient cognition. A mean T-score of 50 and a standard deviation of 10 reflects the T-score on a general population.

The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment. On-treatment is defined as the period of 1st drug administration/1st resumed dose after interruption until last drug administration + REP.

MMRM with fixed effects treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was the repeated measure.

Randomized set. Patients on off-treatment period due to temporary treatment discontinuation or early permanent treatment discontinuation were excluded from the analysis. One patient randomized in error was excluded.

End point type	Primary
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End point timeframe:

MMRM included measurements at baseline, Week 12, and Week 26. Change from baseline values at Week 26 is reported.

End point values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	294		
Units: Units on a scale				
least squares mean (standard error)	2.283 ($\pm$ 0.3094)	2.22 ($\pm$ 0.3065)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
MMRM, including the fixed effects: treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was the repeated measure with an unstructured covariance structure to model the within-patient measurements.	
Comparison groups	Iclepertin 10 mg v Placebo-matching Iclepertin 10 mg
Number of subjects included in analysis	582
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.8854 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.793
upper limit	0.918
Variability estimate	Standard error of the mean
Dispersion value	0.4355

Notes:

[1] - The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment.

[2] - Null hypothesis: The adjusted mean change from baseline to Week 26 in MCCB overall composite T-score in iclepertin 10mg is worse than or equal to that in placebo.

one-sided $p < 0.025$ required for testing subsequent key secondary endpoint hypotheses

Secondary: Key secondary endpoint: Change from baseline in the Schizophrenia Cognition Rating Scale (SCoRS) interviewer total score after 26 weeks of treatment

End point title	Key secondary endpoint: Change from baseline in the Schizophrenia Cognition Rating Scale (SCoRS) interviewer total score after 26 weeks of treatment
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End point description:

The SCoRS is an interview-based assessment tool evaluating cognitive function. It is composed of 20 items on a 7-point scale, ranging from 20 to 140 points, where a higher score indicates a greater cognitive impairment.

The estimated treatment effect included the effect of any concomitant therapies and partner change in

SCoR assessment for all randomized patients on-treatment. On-treatment is defined as the period of 1st drug administration/1st resumed dose after interruption until last drug administration + REP.

MMRM with fixed effects treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was the repeated measure.

Randomized set. Patients on off-treatment period due to temporary treatment discontinuation or early permanent treatment discontinuation were excluded from the analysis of this endpoint. One patient randomized in error was excluded.

End point type	Secondary
End point timeframe:	
MMRM included measurements at baseline, Week 12, and Week 26. Change from baseline values at Week 26 is reported.	

End point values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	292		
Units: Units on a scale				
least squares mean (standard error)	-5.246 ($\pm$ 0.4150)	-5.480 ($\pm$ 0.4140)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

MMRM including the fixed effects: treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

Comparison groups	Iclepertin 10 mg v Placebo-matching Iclepertin 10 mg
Number of subjects included in analysis	584
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.6902
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.234
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.918
upper limit	1.386
Variability estimate	Standard error of the mean
Dispersion value	0.5867

Notes:

[3] - The estimated treatment effect included the effect of any concomitant therapies and partner change in SCoR assessment for all randomized patients on-treatment.

Secondary: Key secondary endpoint: Change from baseline to Week 26 in the adjusted total time T-score in the Virtual Reality Functional Capacity Assessment Tool (VRFCAT)

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

The VRFCAT is a computerized assessment measuring functional capacity of a person performing everyday tasks. It measures the time taken to complete tasks. The lower the VRFCAT T-score, the better patient's functional capacity. A general population has a mean T-score of 50 and a standard deviation of 10.

The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment. On-treatment is defined as the period of 1st drug administration/1st resumed dose after interruption until last drug administration + REP.

MMRM with fixed effects treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was the repeated measure.

Randomized set. Patients on off-treatment period due to temporary treatment discontinuation or early permanent treatment discontinuation were excluded from the analysis. One patient randomized in error and excluded.

End point type	Secondary
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End point timeframe:

MMRM included measurements at baseline, Week 12, and Week 26. Change from baseline values at Week 26 is reported.

End point values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	296		
Units: Units on a scale				
least squares mean (standard error)	3.108 ($\pm$ 0.8089)	3.652 ($\pm$ 0.8018)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

MMRM including the fixed effects: treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

Comparison groups	Iclepertin 10 mg v Placebo-matching Iclepertin 10 mg
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.6334
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.543

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	1.694
Variability estimate	Standard error of the mean
Dispersion value	1.1388

Notes:

[4] - The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment.

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

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

The Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) score evaluates how cognitive difficulties impact the daily life of individuals with schizophrenia. It was composed of 28 items and the total score was derived by calculating the average score of the first 26 items.

The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment. On-treatment is defined as the period of 1st drug administration/1st resumed dose after interruption until last drug administration + REP.

MMRM with fixed effects treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was the repeated measure.

Randomized set. Patients on off-treatment period due to temporary treatment discontinuation or early permanent treatment discontinuation were excluded from the analysis. One patient randomized in error was excluded.

End point type	Secondary
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End point timeframe:

MMRM included measurements at Visit 1a (Week -2/Week -1), Week 15, and Week 24. Change from Visit 1a values at Week 24 is reported.

End point values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	292		
Units: Units on a scale				
least squares mean (standard error)	-0.258 (± 0.0317)	-0.305 (± 0.0316)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

MMRM including the fixed effects: treatment at each visit, stratification factor using the screening MCCB overall composite T-score, and baseline MCCB overall composite T-score at each visit. Visit was treated

as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

Comparison groups	Iclepertin 10 mg v Placebo-matching Iclepertin 10 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.2902
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.135
Variability estimate	Standard error of the mean
Dispersion value	0.0448

Notes:

[5] - The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment.

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

End point title	Change from baseline in the T-score of the number of correct responses on Tower of London at Week 26
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End point description:

The ToL measures the number of correct responses solving an exercise consisting on matching a target ball configuration. The higher the ToL T-score, the better patient's cognitive function. A mean T-score of 50 and a standard deviation of 10 reflects the T-score in a general population.

The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment. On-treatment is defined as the period of 1st drug administration/1st resumed dose after interruption until last drug administration + REP.

ANCOVA with fixed effects treatment, stratification factor of screening MCCB overall composite T-score, and baseline number of correct responses on Tower of London T-score.

Randomized set. Patients on off-treatment period due to temporary treatment discontinuation or early permanent treatment discontinuation were excluded from the analysis. One patient randomized in error was excluded.

End point type	Secondary
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End point timeframe:

At baseline and at Week 26.

End point values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	279		
Units: Units on a scale				
least squares mean (standard error)	1.103 (± 0.6547)	0.475 (± 0.6477)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: ANCOVA with fixed effects treatment, stratification factor of screening MCCB overall composite T-score, and baseline number of correct responses on Tower of London T-score.	
Comparison groups	Iclepertin 10 mg v Placebo-matching Iclepertin 10 mg
Number of subjects included in analysis	552
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.4956
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.628
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.181
upper limit	2.437

Notes:

[6] - The estimated treatment effect included the effect of any concomitant therapies for all randomized patients on-treatment.

Secondary: Ocular safety sub-study: Humphrey Visual Field 24-2 Swedish Interactive Thresholding Algorithm (SITA) Standard

End point title	Ocular safety sub-study: Humphrey Visual Field 24-2 Swedish Interactive Thresholding Algorithm (SITA) Standard
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End point description:

The Humphrey Visual Field 24-2 SITA Standard is a diagnostic test to measure visual fields, or perimetry. The Humphrey visual field test measures the entire area of peripheral vision that can be seen while the eye is focused on a central point. During this test, lights of varying intensities appear in different parts of the visual field while the patient's eye is focused on a central spot. The perception of these lights is charted and then compared to results of a healthy eye at the same age of the patient to determine if any damage has occurred. The tests ranks from 0 to 100%, where 0 means no vision and 100 means perfect vision.

Ocular sub-study set: all treated patients who consented to participate in the ocular sub-study. Only patients with measurements were included in the analysis.

End point type	Secondary
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End point timeframe:

At baseline and at Week 24.

End point values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	21		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Left eye - baseline	93.83 (± 8.82)	95.62 (± 5.56)		
Right eye - baseline	95.87 (± 5.60)	95.87 (± 5.60)		
Left eye - Week 24	94.48 (± 10.69)	96.00 (± 6.58)		
Right eye - Week 24	95.83 (± 5.69)	95.83 (± 5.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular safety sub-study: Central retinal thickness as measured by Spectral domain optical coherence tomography (SD-OCT)

End point title	Ocular safety sub-study: Central retinal thickness as measured by Spectral domain optical coherence tomography (SD-OCT)
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End point description:

The central retinal thickness for both eyes was measured by high-definition optical coherence tomography (spectral domain OCT), which evaluates the retinal and sub-retinal structures of both eyes.

Ocular sub-study set: all treated patients who consented to participate in the ocular sub-study. Only patients with measurements were included in the analysis.

End point type	Secondary
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End point timeframe:

At baseline and at Week 24.

End point values	Iclepertin 10 mg	Placebo-matching Iclepertin 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	21		
Units: Micrometer				
arithmetic mean (standard deviation)				
Left eye - baseline	231.52 (± 26.51)	230.38 (± 26.64)		
Right eye - baseline	233.12 (± 31.03)	235.00 (± 25.45)		
Left eye - Week 24	237.67 (± 27.32)	236.10 (± 25.96)		
Right eye - Week 24	235.46 (± 27.81)	240.49 (± 26.89)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From randomization until individual end of study. Up to 246 days.

Adverse events: From 1st drug administration to last administration, plus residual effect period OR 1st drug administration on the extension trial. Up to 230 days.

Adverse event reporting additional description:

Treated Set (TS): all patients who signed informed consent and were treated with at least one dose of the trial medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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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 / 307 (5.21%)	12 / 312 (3.85%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (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			
Toxicity to various agents			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 307 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Central serous chorioretinopathy			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 307 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 307 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			

subjects affected / exposed	6 / 307 (1.95%)	5 / 312 (1.60%)	
occurrences causally related to treatment / all	2 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	6 / 307 (1.95%)	2 / 312 (0.64%)	
occurrences causally related to treatment / all	0 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 307 (0.33%)	2 / 312 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia aspiration			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 312 (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	Iclepertin 10 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 307 (29.64%)	81 / 312 (25.96%)	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 307 (8.79%)	22 / 312 (7.05%)	
occurrences (all)	32	50	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	22 / 307 (7.17%)	17 / 312 (5.45%)	
occurrences (all)	22	17	

Insomnia subjects affected / exposed occurrences (all)	16 / 307 (5.21%) 17	10 / 312 (3.21%) 10	
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	16 / 307 (5.21%) 17	8 / 312 (2.56%) 8	
Nasopharyngitis subjects affected / exposed occurrences (all)	16 / 307 (5.21%) 16	21 / 312 (6.73%) 26	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 307 (3.58%) 12	16 / 312 (5.13%) 20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2022	Global Amendment 1: substance name "BI 425809" replaced by "iclepertin"; Key secondary efficacy endpoint VRFCAT updated to include T-score; clarified that the key secondary efficacy endpoint for the VRFCAT is the total adjusted time T-score; clarified that study partner is required for SCoRS and PANSS interviews at least at Visit 2 and end of trial (EoT); changed the requirement for ophthalmologic assessments to be performed for all ocular AEs, rather than only moderate to severe vision-related AEs; clarified that Paxlovid™ should not be used concomitantly with the trial medication and that patients who required treatment with Paxlovid should be temporarily discontinued from trial medication; revised the further endpoint for health care resource utilization (HCRU) to include the number of any health care visits due to the underlying disease during the on-treatment period; inclusion criterion #5 updated to require patients taking 2 antipsychotic medications to be taking at least one with a dose within the approved label dose range and the other not to exceed the maximum daily dose per local label; inclusion criterion #6 updated to remove reference to hypnotic load up to 0.25 mg brotizolam equivalence and clarified that other psychoactive medications could not exceed the maximum daily dose per local label; exclusion criterion #2 updated to exclude potential patients with epilepsy; exclusion criterion #8 updated to exclude the use of esketamine as well as ketamine; exclusion criterion #10 updated to exclude potential patients previously treated with iclepertin, however, patients who may have screen failed in another trial with iclepertin could be considered for the CONNEX trial; exclusion criterion #11 updated to indicate that potential patients who were taking antiepileptic medications for the treatment of epilepsy were to be excluded, however, taking antiepileptic medications as monotherapy to treat other conditions was allowed (continues)
28 October 2022	Global amendment 1 (continued): exclusion criterion #18 updated to exclude potential patients who had anaemia; exclusion criterion #26 (excluding potential patients with an allergy to iclepertin and/or any of the excipients) updated to refer to the Investigator's Brochure for the list of ingredients in iclepertin and placebo; added guidance related to patients who were lost to follow-up and included a reference to the retention guide; removed the requirement to follow patients after permanent discontinuation of trial treatment until EoT plus 28 days; revised the list of reasons for withdrawing individual patients from trial treatment to include needing to take restricted medications; removed quetiapine as an example of restricted sedative medication; clarified restriction on short term use of opioids for pain, cough, or diarrhoea; added vaccination for COVID-19 to the permitted therapies; allowed re-testing for urine drug screen at Visit 1a if results were positive at Visit 1; added requirement that all patients consent to use the adherence monitoring application at screening but allowed randomised patients on treatment who refused to continue using the application to remain in the trial; clarified that duplication check would be used only for countries that had not opted out by local amendment; clarified that patients could start trial procedures after providing written informed consent even if the study partner informed consent was not yet signed; clarified the procedures for rolling over into the extension trial; clarified that the randomised set would exclude patients randomised in error and discontinued from the trial before the start of trial medication; updated the statistical model, revised wording to indicate that the caregiver would be asked to complete the additional questionnaires; clarified that in case of exceptional circumstances such as the COVID-19 pandemic, secondary endpoint assessments could not be performed remotely as it would reduce quality.
22 December 2022	Global amendment 2: Substance name "BI 425809" replaced by "iclepertin" in places where this change was not made in Amendment 1; Reference literature for Placebo Control Reminder Script was added, as it was mistakenly omitted in Amendment 1.

19 September 2023	Global amendment 3: Updated address of Coordinating Investigator; added footnote to the Flow Chart to state that Columbia Suicide Severity Rating Scale (C-SSRS) could be repeated based on investigator discretion; based on DMC recommendation, reinforced documenting details of any positive suicidal ideation and providing comments on clinical significance and any additional follow-up action items; also added that the C-SSRS could be repeated at an unscheduled visit based on investigator discretion; added substance use to the Flow Chart; clarified calculation of treatment compliance based on tablets removed from blisters; added text to clarify the time schedule of PK blood sampling and added reminder that actual times were to be collected in the electronic case report form (CRF).
25 June 2024	Global amendment 4: Change of coordinating investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported