



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-3)

Summary

EudraCT number	2020-003726-23
Trial protocol	DE DK FI CZ BE LT PT AT BG
Global end of trial date	20 November 2024

Results information

Result version number	v1 (current)
This version publication date	13 November 2025
First version publication date	13 November 2025

Trial information

Trial identification

Sponsor protocol code	1346-0013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04860830
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	20 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2024
Global end of trial reached?	Yes
Global end of trial date	20 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study 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 of this study was to assess the efficacy in daily functioning using Schizophrenia Cognition Rating Scale (SCoRS) and Virtual Reality Functional Capacity Assessment Tool (VRFCAT) in patients with schizophrenia treated for 26-week treatment with Iclepertin 10 mg as compared with placebo.

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. All subjects and study partners signed informed consent forms 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	09 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: 91
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	China: 152
Country: Number of subjects enrolled	Czechia: 44
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Lithuania: 18
Country: Number of subjects enrolled	Mexico: 58
Country: Number of subjects enrolled	Portugal: 4

Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	Taiwan: 70
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 209
Worldwide total number of subjects	844
EEA total number of subjects	159

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)	844
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multi-center, multi-national, randomized, double-blind, placebo controlled, parallel group, 26-week trial in subjects with schizophrenia on stable antipsychotic treatment. Subjects who completed the trial could directly enroll into an extension trial (1346-0014). A sub-study was conducted in several countries to investigate ocular safety.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation and attended a specialist site which ensured that they strictly met all inclusion and no exclusion criteria. Of 609 enrolled subjects, 2 were randomised in error (1 to each arm) and not treated.

Period 1

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

Blinding implementation details:

Except for independent DMC, subjects, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regards to the randomized treatment assignments until the database was declared ready for analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iclepertin 10 mg

Arm description:

Patients with schizophrenia took one tablet of 10 milligram (mg) iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.

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 once daily for 26 weeks

Arm title	Placebo
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Arm description:

Patients with schizophrenia took one tablet of placebo matching iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.

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 daily for 26 weeks

Number of subjects in period 1^[1]	Iclepertin 10 mg	Placebo
Started	302	305
Treated	301	305
Ocular safety sub-study	36 ^[2]	38 ^[3]
Completed	271	258
Not completed	31	47
Physician decision	1	-
Adverse event, non-fatal	8	18
Subject decision	9	12
Perceived lack of efficacy	1	6
No reason available	3	2
Burden of study procedures	2	4
Change of residence	4	2
Other than listed	2	3
Not treated	1	-

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 the 844 subjects enrolled in the trial, 607 were correctly randomized.

[2] - 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: Out of the 302 subjects randomized to this treatment, 36 participated in a sub-study.

[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: Out of the 305 subjects randomized to this treatment, 38 participated in a sub-study.

Baseline characteristics

Reporting groups

Reporting group title	Iclepertin 10 mg
Reporting group description:	
Patients with schizophrenia took one tablet of 10 milligram (mg) iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.	
Reporting group title	Placebo
Reporting group description:	
Patients with schizophrenia took one tablet of placebo matching iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.	

Reporting group values	Iclepertin 10 mg	Placebo	Total
Number of subjects	302	305	607
Age categorical			
Randomized Set (RS): all patients who signed informed consent and were randomized into the trial, regardless of whether they were treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS.			
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)	302	305	607
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Randomized Set (RS): all patients who signed informed consent and were randomized into the trial, regardless of whether they were treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS.			
Units: years			
arithmetic mean	34.3	33.4	
standard deviation	± 8.7	± 8.8	-
Sex: Female, Male			
Randomized Set (RS): all patients who signed informed consent and were randomized into the trial, regardless of whether they were treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS.			
Units: Subjects			
Female	94	130	224
Male	208	175	383
Race (NIH/OMB)			
Randomized Set (RS): all patients who signed informed consent and were randomized into the trial, regardless of whether they were treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS.			
Units: Subjects			
American Indian or Alaska Native	10	7	17
Asian	112	116	228

Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	27	24	51
White	149	155	304
More than one race	3	3	6
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomized Set (RS): all patients who signed informed consent and were randomized into the trial, regardless of whether they were treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication were excluded from the RS.			
Units: Subjects			
Hispanic or Latino	71	83	154
Not Hispanic or Latino	231	222	453
Unknown or Not Reported	0	0	0
Overall composite T-score of the MATRICS consensus cognitive battery (MCCB)			
The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB) assesses 7 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. T-scores in the general population have a mean of 50 and standard deviation of 10, and a higher score indicates better cognition. Randomized Set (RS).			
Units: T-score			
arithmetic mean	29.4	29.8	
standard deviation	± 14.1	± 13.5	-

End points

End points reporting groups

Reporting group title	Iclepertin 10 mg
Reporting group description: Patients with schizophrenia took one tablet of 10 milligram (mg) iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.	
Reporting group title	Placebo
Reporting group description: Patients with schizophrenia took one tablet of placebo matching iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.	

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
End point description: The MCCB assesses 7 cognitive domains, including speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. T-scores in the general population have a mean of 50 and standard deviation of 10, and a higher score indicates better cognition. The primary analysis was a restricted maximum likelihood (REML) based approach using a mixed-effects model for repeated measurements (MMRM), which included the fixed categorical effects of treatment at each visit, fixed categorical effect of the stratification factor using the screening MCCB overall composite T-score, and a fixed effect for the continuous covariate of baseline at each visit. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within-subject dependencies. Intercurrent events were addressed using different pre-defined strategies. Randomized Set (RS).	
End point type	Primary
End point timeframe: The MMRM model incorporates values from baseline (Week 0), Week 12 and Week 26. The data represent the Least Squares Means at Week 26.	

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	305		
Units: T-score				
least squares mean (standard error)	1.890 ($\pm$ 0.3336)	2.273 ($\pm$ 0.3372)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The primary analysis was a REML-based approach using a MMRM, which included the fixed categorical effects of treatment at each visit, fixed categorical effect of the stratification factor using the screening MCCB overall composite T-score, and a fixed effect for the continuous covariate of baseline at each visit. Visit was treated as the repeated measure with an unstructured covariance structure used to model the within-subject dependencies.

Comparison groups	Iclepertin 10 mg v Placebo
Number of subjects included in analysis	607
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.4187 ^[2]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-0.384
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.316
upper limit	0.548
Variability estimate	Standard error of the mean
Dispersion value	0.4745

Notes:

[1] - Adjusted mean iclepertin - adjusted mean placebo

[2] - Null hypothesis: the adjusted mean change in iclepertin is worse than or equal to that in placebo. One-sided significance level of <0.025 is needed for conducting further formal hypothesis tests in the secondary endpoints.

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

End point title	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:

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. Higher ratings reflect a greater degree of impairment. The interviewer integrates information from separate patient and study partner interviews to generate a total score, which ranges from 20 to 80. The analysis was a REML-based approach using a MMRM model, which 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, a fixed effect for the continuous covariate of baseline 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. Intercurrent events were addressed using different pre-defined strategies. Randomized Set (RS).

End point type	Secondary
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End point timeframe:

The MMRM model incorporates values from baseline (Week 0), Week 12 and Week 26. The data represent the Least Squares Means at Week 26.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	305		
Units: Scores on a scale				
least squares mean (standard error)	-3.751 (± 0.3697)	-4.513 (± 0.3728)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The analysis was a REML-based approach using a MMRM model, which 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, a fixed effect for the continuous covariate of baseline 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	607
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.1478
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	0.762
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.271
upper limit	1.794
Variability estimate	Standard error of the mean
Dispersion value	0.5255

Notes:

[3] - Adjusted mean iclepertin - adjusted mean placebo

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

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

The VRFCAT is a virtual reality shopping trip performed on a tablet, and was used as an electronic Functional Capacity measure by measuring the total time adjusting for the number of errors. T-scores in the general population have a mean of 50 and standard deviation of 10, and a higher score indicates a better functional outcome. The analysis was a REML-based approach using a MMRM model, which 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, a fixed effect for the continuous covariate of baseline 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. Intercurrent events were addressed using different pre-defined strategies. Randomized Set (RS).

End point type	Secondary
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End point timeframe:

The MMRM model incorporates values from baseline (Week 0), Week 12 and Week 26. The data represent the Least Squares Means at Week 26.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	305		
Units: T-score				
least squares mean (standard error)	1.820 ($\pm$ 0.7633)	3.042 ($\pm$ 0.7669)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The analysis was a REML-based approach using a MMRM model, which 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, a fixed effect for the continuous covariate of baseline 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	607
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.2596
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-1.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.347
upper limit	0.904
Variability estimate	Standard error of the mean
Dispersion value	1.082

Notes:

[4] - Adjusted mean iclepertin - adjusted mean placebo

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

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

This is an Executive Functions/Reasoning and Problem Solving test where patients were shown two images on opposite sides of a tablet screen. Each image showed a different configuration of 3 colored balls arranged on 3 pegs. Patients were 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 employed in tower tests. T-scores in the general population have a mean of 50 and standard deviation of 10, and a higher score indicates a better outcome.

The analysis was performed with an analysis of covariance (ANCOVA) model, which included treatment, stratification factor of screening MCCB overall composite T-score (< 30 , ≥ 30), and baseline number of correct responses on Tower of London T-score. Randomized Set (RS). Only patients with available data

at Week 26 were included in the analysis.

End point type	Secondary
End point timeframe:	
At baseline (Week 0) and at Week 26.	

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	277		
Units: T-score				
least squares mean (standard error)	0.440 ($\pm$ 0.5773)	1.016 ($\pm$ 0.5805)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The analysis was performed with an ANCOVA model, which included treatment, stratification factor of screening MCCB overall composite T-score (< 30 , ≥ 30), and baseline number of correct responses on Tower of London T-score.	
Comparison groups	Iclepertin 10 mg v Placebo
Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.4822
Method	ANCOVA
Parameter estimate	Difference of adjusted means
Point estimate	-0.576
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.184
upper limit	1.032
Variability estimate	Standard error of the mean
Dispersion value	0.8187

Notes:

[5] - Adjusted mean iclepertin - adjusted mean placebo

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:

PRECIS consists of 26 items covering 6 domains (memory, communication, self-control, executive function, attention, sharp thinking), and 2 additional items assessing the overall degree of bother associated with all domains. Questions are answered via a 5-category Likert scale, with higher scores indicating a worse patient experience. The total score, ranging from 26 to 130, is the average score of the first 26 items. The analysis was a REML-based approach using a MMRM model, which 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. Intercurrent events were addressed using different pre-defined strategies. RS.

End point type	Secondary
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End point timeframe:

The MMRM model incorporates values from baseline (screening), Week 15 and Week 24. The data represent the Least Squares Means at Week 24.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	305		
Units: Scores on a scale				
least squares mean (standard error)	-0.275 ($\pm$ 0.0274)	-0.234 ($\pm$ 0.0278)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The analysis was a REML-based approach using a MMRM model, which 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	607
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.2936
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.118
upper limit	0.036
Variability estimate	Standard error of the mean
Dispersion value	0.0391

Notes:

[6] - Adjusted mean iclepertin - adjusted mean placebo

Secondary: Ocular safety sub-study: Change from baseline in Humphrey visual field 24-2 Swedish Interactive Thresholding Algorithm (SITA) standard at Week 24

End point title	Ocular safety sub-study: Change from baseline in Humphrey visual field 24-2 Swedish Interactive Thresholding Algorithm (SITA) standard at Week 24
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End point description:

The Humphrey visual field 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. Visual field Index goes from 100%= perfect to 0= no vision.

Ocular sub-study Set (EYE): all treated patients who consented to participate in the ocular sub-study (including late/retrospective consent to the ocular sub-study) and had evaluable ophthalmologic measurements.

End point type	Secondary
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End point timeframe:

Measurements were performed at baseline (screening) and at Week 24.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	32		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Left eye	2.00 (± 6.06)	-3.97 (± 12.99)		
Right eye	-0.31 (± 3.56)	-4.44 (± 15.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular safety sub-study: Change from baseline in spectral domain ocular coherence tomography (OCT)

End point title	Ocular safety sub-study: Change from baseline in spectral domain ocular coherence tomography (OCT)
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End point description:

The central retinal thickness measurements were recorded for each eye via high definition optical coherence tomography (spectral domain OCT) to evaluate the retinal and sub-retinal structures.

Ocular sub-study Set (EYE): all treated patients who consented to participate in the ocular sub-study (including late/retrospective consent to the ocular sub-study) and had evaluable ophthalmologic measurements.

End point type	Secondary
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End point timeframe:

Measurements were performed at baseline (screening) and at Week 24.

End point values	Iclepertin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	32		
Units: Micrometer (µm)				
arithmetic mean (standard deviation)				
Left eye	-1.57 (± 7.25)	-1.47 (± 10.08)		
Right eye	-1.14 (± 5.70)	-2.41 (± 11.75)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first treatment administration until last treatment administration plus residual effect period, up to approximately 31 weeks.

Adverse event reporting additional description:

Treated Set (TS): includes 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	27.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Patients with schizophrenia took one tablet of placebo matching iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.

Reporting group title	Iclepertin 10 mg
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Reporting group description:

Patients with schizophrenia took one tablet of 10 milligram (mg) iclepertin orally once daily for 26 weeks. Patients were permitted to remain on other antipsychotic and psychotropic medications, as specified in the eligibility criteria.

Serious adverse events	Placebo	Iclepertin 10 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 305 (4.59%)	13 / 301 (4.32%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Limb crushing injury			
subjects affected / exposed	1 / 305 (0.33%)	0 / 301 (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	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			

subjects affected / exposed	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 305 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 305 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
subjects affected / exposed	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			

subjects affected / exposed	2 / 305 (0.66%)	3 / 301 (1.00%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	2 / 305 (0.66%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	6 / 305 (1.97%)	3 / 301 (1.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 305 (0.33%)	0 / 301 (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			
Hydronephrosis			
subjects affected / exposed	1 / 305 (0.33%)	0 / 301 (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			
Bronchiolitis			
subjects affected / exposed	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 305 (0.33%)	0 / 301 (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	0 / 305 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 305 (0.00%)	1 / 301 (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	65 / 305 (21.31%)	68 / 301 (22.59%)	
Investigations			
Weight increased			
subjects affected / exposed	20 / 305 (6.56%)	11 / 301 (3.65%)	
occurrences (all)	20	11	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 305 (7.21%)	28 / 301 (9.30%)	
occurrences (all)	25	40	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	11 / 305 (3.61%)	20 / 301 (6.64%)	
occurrences (all)	12	20	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 305 (6.23%)	17 / 301 (5.65%)	
occurrences (all)	22	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2020	Correction of the inconsistent trial number in protocol header.
04 November 2022	Part 1. The amendment included the following main changes: 1) substance name "BI 425809" replaced by "iclepertin"; 2) clarified that the key secondary efficacy endpoint for the VRFCAT is the total adjusted time T-score; 3) clarified that study partner is required for SCoRS and Positive and Negative Syndrome Scale (PANSS) interviews at least at Visit 2 and End of treatment (EOT); 4) changed the requirement for ophthalmologic assessments to be performed for all ocular adverse events (AEs), rather than only moderate to severe vision-related AEs; 5) 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; 6) revision of a further endpoint; 7) updates to inclusion and exclusion criteria; 8) added guidance related to patients who were lost to follow-up and included a reference to the retention guide; 9) removed the requirement to follow patients after permanent discontinuation of trial treatment until EOT plus 28 days; 10) revised the list of reasons for withdrawing individual patients from trial treatment to include needing to take restricted medications; 11) removed quetiapine as an example of restricted sedative medication; 12) clarified restriction on short term use of opioids for pain, cough, or diarrhoea; 13) added vaccination for Coronavirus disease 2019 (COVID-19) to the permitted therapies; 14) allowed re-testing for urine drug screen at Visit 1a if results were positive at Visit 1; 15) added requirement that all patients consent to use the AiCure application at screening but allowed randomised patients on treatment who refused to continue using the application to remain in the trial; 16) clarified that Verified Clinical Trials would be used only for countries that had not opted out by local amendment.
04 November 2022	Part 2. 17) removal of examples of scales that should be done by the same rater; clarified that ideally, all scales should be performed by the same rater whenever possible; 18) clarified that the clinical global impression used in the trial should be based on the global impression including the patient's functioning based on the SCoRS assessment; 19) clarified that patients could start trial procedures after providing written informed consent even if the study partner informed consent was not yet signed; 20) clarified the procedures for rolling over into the extension trial; 21) clarified that the randomised set would exclude patients randomised in error and discontinued from the trial before the start of trial medication; 22) updated the statistical model; 23) revised wording to indicate that the caregiver would be asked to complete the additional questionnaires; 24) 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.
18 September 2023	The amendment included the following main changes: 1) added footnote to the Flow Chart to state that Columbia Suicide Severity Rating Scale (C-SSRS) could be repeated based on investigator discretion; 2) 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; 3) added substance use to the Flow Chart; 4) clarified calculation of treatment compliance based on tablets removed from blisters; 5) added text to clarify the time schedule of pharmacokinetic blood sampling and added reminder that actual times were to be collected in the electronic case report form (eCRF).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported