Clinical trial results:
A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome

Summary

EudraCT number	2016-004973-42
Trial protocol	GB
Global end of trial date	07 April 2021

Results information

Result version number	v1
This version publication date	12 February 2022
First version publication date	12 February 2022

Trial information

Trial identification

Sponsor protocol code	1289.32

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03230097
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	29 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2021
Global end of trial reached?	Yes
Global end of trial date	07 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to investigate the efficacy, safety, and tolerability of BI 409306 compared with placebo given for 52 weeks to patients with attenuated psychosis syndrome (APS). The study was designed to show superiority of BI 409306 over placebo in achieving remission from APS, as well as improvement in cognition and functional capacity.

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	17 October 2017
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	United States: 45
Country: Number of subjects enrolled	China: 1
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	50
EEA total number of subjects	0

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)	5
Adults (18-64 years)	45

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised, placebo-controlled, double-blind, parallel group trial over 52 weeks. The patients were randomised to 1 of the 2 treatment groups at a ratio of 1:1. After completion of the treatment period, or following early discontinuation, patients were to complete a 4-weeks follow-up period.

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 409306

Arm description:

Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	BI 409306
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Arm title	Placebo

Arm description:

Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took placebo matching 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately

the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Number of subjects in period 1	BI 409306	Placebo
Started	24	26
Completed	9	10
Not completed	15	16
Consent withdrawn by subject	7	3
Adverse event, non-fatal	2	1
Covid-19 pandemic outbreak	-	1
outcome event	-	1
Lost to follow-up	2	4
Trial termination	4	5
non-compliance	-	1

Baseline characteristics

Reporting groups	
Reporting group title	BI 409306
Reporting group description:	
Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took placebo matching 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.	

Reporting group values	BI 409306	Placebo	Total
Number of subjects	24	26	50
Age categorical			
The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
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)	1	4	5
Adults (18-64 years)	23	22	45
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: years			
arithmetic mean	23.4	20.9	
standard deviation	± 4	± 3.8	-
Sex: Female, Male			
The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: participants			
Female	12	13	25
Male	12	13	25
Race (NIH/OMB)			
The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	4

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	2	6
White	16	21	37
More than one race	1	1	2
Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB)			
The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
Hispanic or Latino	5	2	7
Not Hispanic or Latino	19	24	43
Unknown or Not Reported	0	0	0
Schizophrenia Cognition Rating Scale (SCoRS) total score			
The SCoRS is a 20-item interview-based assessment of cognitive deficits and the degree to which they affect day-to-day functions. It collects information from a patient interview, interview with an informant (if available), and the administering clinician. Each of the 20 items of the SCoRS is rated on a 4-point scale (minimum score of 1 and maximum of 4). Higher ratings reflect a greater degree of impairment. The composite score will be the sum of the 20 items (minimum score of 20 and maximum of 80). TS.			
Units: Score on a scale			
arithmetic mean	36.333	36.462	
standard deviation	± 7.405	± 7.814	-
Brief Assessment of Cognition (BAC App) composite T score			
Brief Assessment of Cognition (BAC App) composite T score (averages five of the standardized scaled sub-test scores, token motor test score not included). The BACS consists of five tests assessing multiple domains of cognitive function: Verbal Memory, Digit Sequencing, Semantic and Letter Fluency, Symbol Coding, and Tower of London. A composite T score that is calculated using the five standardized scaled sub-test scores will be generated, larger T-score indicates better cognition.			
Units: Score on a scale			
arithmetic mean	52.417	49.308	
standard deviation	± 7.945	± 13.451	-
Positive Syndrome Scale (PANSS)			
The PANSS positive symptom scales has 7 items, and the General Psychopathology Scale (not reported) has 16 items. The patient is rated from 1 to 7 on the 30 different items based on the interview, as well as reports from an informant when possible. The total score is the summation of the 30 item scores (minimum of 30 and maximum of 210) where a lower score represents an improvement in schizophrenia symptoms. TS.			
Units: Score on a scale			
arithmetic mean	16.0	14.5	
standard deviation	± 3.9	± 3.4	-
Negative Syndrome Scale (PANSS)			
The PANSS negative symptom scales has 7 items, and the General Psychopathology Scale (not reported) has 16 items. The patient is rated from 1 to 7 on the 30 different items based on the interview, as well as reports from an informant when possible. The total score is the summation of the 30 item scores (minimum of 30 and maximum of 210) where a lower score represents an improvement in schizophrenia symptoms.The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: Score on a scale			
arithmetic mean	14.4	13.4	
standard deviation	± 5.1	± 3.3	-
Positive and Negative Syndrome Scale (PANSS)			
The PANSS positive and negative symptom scales each have 7 items, and the General Psychopathology Scale has 16 items. The patient is rated from 1 to 7 on the 30 different items based on the interview, as well as reports from an informant when possible. The total score is the summation of the 30 item scores			

where a lower score represents an improvement in schizophrenia symptoms. The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: Score on a scale			
arithmetic mean	62.8	58.2	
standard deviation	± 12.5	± 11.0	-

End points

End points reporting groups

Reporting group title	BI 409306

Reporting group description:

Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Reporting group title	Placebo

Reporting group description:

Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took placebo matching 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Primary: Time to remission from attenuated psychosis syndrome (APS) within a 52-week timeframe

End point title	Time to remission from attenuated psychosis syndrome (APS) within a 52-week timeframe

End point description:

Time to remission from attenuated psychosis syndrome (APS) within a 52-week timeframe. The incidence rate per patient-years of remission from attenuated psychosis syndrome (APS) is reported. Remission from APS is defined as a score of <3 on all of the five Positive Symptom items of the Scale of Prodromal Symptoms (SOPS) and maintained until the end of treatment. The SOPS provides a 6-point scale (minimum of 0 and maximum of 6, higher score indicating worse symptoms) to quantitatively rate the severity of five attenuated positive symptoms.
Full Analysis Set (FAS): All patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment and who have analysable data (observed or imputed) in at least one efficacy endpoint.

End point type	Primary

End point timeframe:

Up to 52 weeks

End point values	BI 409306	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Incidence rate per patient-years				
number (not applicable)	0.433	0.446		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified (by baseline use of antipsychotic medication) Cox proportional hazards model was used. Treatment effect and NAPLS risk score as covariates.

Comparison groups	BI 409306 v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7873
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.849
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.258
upper limit	2.795

Secondary: Time to first episode of psychosis

End point title	Time to first episode of psychosis

End point description:

Time to first episode of psychosis. The incidence rate per patient-years of psychosis is reported, psychosis is defined as one or more positive Scale of Prodromal Symptoms (SOPS) symptoms rated a 6 AND either a symptom is seriously disorganizing or dangerous OR one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month. OR a new prescription or increase in dose of an ongoing antipsychotic medication. The SOPS provides a 6-point scale (minimum of 0 and maximum of 6, higher score indicating worse symptoms) to quantitatively rate the severity of five attenuated positive symptoms.
Full Analysis Set (FAS): All patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment and who have analysable data (observed or imputed) in at least one efficacy endpoint.

End point type	Secondary

End point timeframe:

Up to 52 weeks.

End point values	BI 409306	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Incidence rate per patient-years				
number (not applicable)	0	0.125		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 24 and 52 weeks of treatment

End point title	Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 24 and 52 weeks of treatment

End point description:

Change from baseline (Day -28 to -7) in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 24 and 52 weeks of treatment. Each of the 20 items of the SCoRS is rated on a 4-point scale (range: 1-4). Higher ratings reflect a greater degree of impairment. The composite score will be the sum of the 20 items (range: 20-80). Data analyzed using the restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM) including fixed, categorical effects of treatment, visit, treatment by visit interaction, baseline North American Prodromal Longitudinal Study (NAPLS) risk score, baseline use of antipsychotic medication and continuous fixed covariates of baseline score and baseline-by-visit interaction. All patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment and who have analysable data for both timepoints.

End point type	Secondary

End point timeframe:

Baseline, week 24 and week 52.

End point values	BI 409306	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[1]	15[2]		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Adjusted mean change from baseline at week 24	-2.12 (-7.721 to 3.484)	-3.89 (-8.925 to 1.148)		
Adjusted mean change from baseline at week 52	-3.05 (-8.881 to 2.778)	-6.23 (-11.530 to -0.927)		

Notes:

[1] - Number of Subjects Analyzed at week 52 = 9.

[2] - Number of Subjects Analyzed at week 52 = 10.

Statistical analyses

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

BI 409306 vs. placebo of change from baseline at week 52. Data analyzed using the restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM) including fixed, categorical effects of treatment, visit, treatment by visit interaction, baseline North American Prodromal Longitudinal Study (NAPLS) risk score, baseline use of antipsychotic medication and continuous fixed covariates of baseline score and baseline-by-visit interaction.

Comparison groups	BI 409306 v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3127
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.071
upper limit	9.425

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

BI 409306 vs. placebo of change from baseline at week 24.Data analyzed using the restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM) including fixed, categorical effects of treatment, visit, treatment by visit interaction, baseline North American Prodromal Longitudinal Study (NAPLS) risk score, baseline use of antipsychotic medication and continuous fixed covariates of baseline score and baseline-by-visit interaction.

Comparison groups	BI 409306 v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5212
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.773
upper limit	7.315

Secondary: Change from baseline in the tablet based Brief Assessment of Cognition (BAC App) composite T score after 52 weeks of treatment

End point title	Change from baseline in the tablet based Brief Assessment of Cognition (BAC App) composite T score after 52 weeks of treatment

End point description:

Change from baseline (Day -28 to -7) in the tablet based Brief Assessment of Cognition (BAC App) composite T score after 52 weeks of treatment. The BAC consists of five tests assessing multiple domains of cognitive function: Verbal Memory, Digit Sequencing, Semantic and Letter Fluency, Symbol Coding, and Tower of London. A composite T score that is calculated using the five standardized scaled sub-test scores was generated (averages five of the standardized scaled sub-test scores, token motor test score not included), larger T-score indicates better cognition. Data analyzed using the restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM) including fixed, categorical effects of treatment, visit, treatment by visit interaction, baseline North American Prodromal Longitudinal Study (NAPLS) risk score, baseline use of antipsychotic medication and continuous fixed covariates of baseline score and baseline-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline and week 52.

End point values	BI 409306	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	10		
Units: Score on a scale				
least squares mean (confidence interval 95%)	-1.51 (-7.950 to 4.929)	3.48 (-1.641 to 8.597)		

Statistical analyses

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

BI 409306 vs. placebo of change from baseline at week 52.
Data analyzed using the restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM) including fixed, categorical effects of treatment, visit, treatment by visit interaction, baseline North American Prodromal Longitudinal Study (NAPLS) risk score, baseline use of antipsychotic medication and continuous fixed covariates of baseline score and baseline-by-visit interaction.

Comparison groups	BI 409306 v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1602
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-4.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.033
upper limit	2.057

Secondary: Change from baseline in Positive and Negative Syndrome Scale (PANSS) positive items score, negative items score, and total score after 52 weeks of treatment

End point title	Change from baseline in Positive and Negative Syndrome Scale (PANSS) positive items score, negative items score, and total score after 52 weeks of treatment

End point description:

Change from baseline (Day -28 to -7) in Positive and Negative Syndrome Scale (PANSS) positive items score, negative items score, and total score after 52 weeks of treatment. The PANSS positive and negative symptom scales each have 7 items, and the General Psychopathology Scale (not reported) has 16 items. The patient is rated from 1 to 7 on the 30 different. Total score is the sum of the 30 item scores (range: 30-210) where a lower score represents an improvement in schizophrenia symptoms. Data analyzed using the REML MMRM including fixed, categorical effects of treatment, visit, treatment by visit interaction, baseline NAPLS risk score, baseline use of antipsychotic medication and continuous fixed covariates of baseline score and baseline-by-visit interaction. Patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment and who have data (observed or imputed) for both timepoints in this endpoint.

End point type	Secondary

End point timeframe:

Baseline and week 52.

End point values	BI 409306	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Change from baseline-week 52, positive items score	-3.83 (-6.355 to -1.296)	-3.03 (-5.312 to -0.743)		
Change from baseline-week 52, negative items score	-0.98 (-3.571 to 1.609)	-2.41 (-4.788 to -0.032)		
Change from baseline-week 52, total score	-6.02 (-14.396 to 2.360)	-7.73 (-15.216 to -0.245)		

Statistical analyses

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

BI 409306 vs. placebo of change from baseline at week 52, positive items score.
Data analyzed using the restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM) including fixed, categorical effects of treatment, visit, treatment by visit interaction, baseline North American Prodromal Longitudinal Study (NAPLS) risk score, baseline use of antipsychotic medication and continuous fixed covariates of baseline score and baseline-by-visit interaction.

Comparison groups	BI 409306 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8691
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.181
upper limit	2.71

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

BI 409306 vs. placebo of change from baseline at week 52, positive items score.
Restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM), see endpoint description for details.

Comparison groups	BI 409306 v Placebo

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5858
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.749
upper limit	2.153

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

BI 409306 vs. placebo of change from baseline at week 52, total score.
Restricted maximum likelihood (REML) mixed effects model with repeated measurements (MMRM), see endpoint description for details.

Comparison groups	BI 409306 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3445
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.604
upper limit	4.462

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From treatment start date until the date of discontinuation of trial medication + 7 days, up to 381 days.

Adverse event reporting additional description:

The treated set (TS) includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	BI 409306

Reporting group description:

Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Reporting group title	Placebo

Reporting group description:

Patients meeting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for attenuated psychosis syndrome (APS) per the Structured Interview for Psychosis-Risk Syndromes (SIPS) took placebo matching 50 milligrams BI 409306, as a film-coated tablet, orally twice a day at approximately the same time every day in the morning and in the evening (approximately 12 hours apart) with or without food for 52 weeks.

Serious adverse events	BI 409306	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal behaviour			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (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	BI 409306	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 24 (87.50%)	16 / 26 (61.54%)	
Investigations			
Weight increased			
subjects affected / exposed	2 / 24 (8.33%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 24 (0.00%)	4 / 26 (15.38%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 24 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Ligament sprain			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 24 (33.33%)	1 / 26 (3.85%)	
occurrences (all)	10	1	
Headache			
subjects affected / exposed	5 / 24 (20.83%)	8 / 26 (30.77%)	
occurrences (all)	5	12	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	3 / 24 (12.50%)	2 / 26 (7.69%)	
occurrences (all)	3	4	
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Eye disorders			
Chromatopsia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Dyschromatopsia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Photophobia			
subjects affected / exposed	8 / 24 (33.33%)	2 / 26 (7.69%)	
occurrences (all)	13	2	
Visual impairment			
subjects affected / exposed	5 / 24 (20.83%)	2 / 26 (7.69%)	
occurrences (all)	7	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 24 (8.33%)	3 / 26 (11.54%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	2 / 24 (8.33%)	2 / 26 (7.69%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	0 / 24 (0.00%)	5 / 26 (19.23%)	
occurrences (all)	0	7	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 24 (4.17%)	4 / 26 (15.38%)	
occurrences (all)	1	5	
Oropharyngeal pain			
subjects affected / exposed	0 / 24 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	4	

Rhinorrhoea			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 24 (20.83%)	1 / 26 (3.85%)	
occurrences (all)	6	1	
Anxiety			
subjects affected / exposed	3 / 24 (12.50%)	2 / 26 (7.69%)	
occurrences (all)	3	3	
Nightmare			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Sleep disorder			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	2	4	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	2 / 24 (8.33%)	1 / 26 (3.85%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2017	This amendment included the following major modifications or additions to the trial conduct: - Patients could be enrolled if they were taking antipsychotic medication during the screening period. If a patient discontinued an antipsychotic medication, they could be randomised 2 weeks after discontinuation - Exclusion criteria were added to define stability of antipsychotic medication - Close monitoring for potential trial drug abuse and/or diversion was introduced - Structured Interview for Psychosis-Risk Syndromes (SIPS)/Scale of Prodromal Symptoms (SOPS) psychometric analyses were added - Electroencephalogram/electroencephalography (EEG) paradigms were adapted to be compatible with the NAPLS2 EEG paradigms
10 July 2017	This amendment included the following addition to the exclusion criteria: - Patients with a history of moderate to severe hepatic impairment (Child-Pugh B/C) or moderate to severe renal impairment (Stage 3 to 5) were excluded from the trial
04 October 2018	This amendment included the following major modifications or additions to the trial conduct: - The primary endpoint was changed to time to remission from Attenuated psychosis syndrome (APS). Remission from APS was defined as a score of <3 on all the P1-P5 Positive Symptom items of the SOPS and maintained until the end of treatment - The original primary endpoint, time to first episode of psychosis as adjudicated by the Central Rating Committee, became a secondary endpoint - Main diagnosis for trial entry was modified: a diagnosis of APS was defined by the presence of recent attenuated positive symptoms that meet all five DSM-5 criteria (A to E) - Exclusion Criteria #2, #6, and 14 were clarified and Criterion #24 was added to exclude patients with hypersensitivity to the excipients in the Investigational medicinal product (IMP)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	Due to the COVID-19 pandemic, the recruitment of new subjects was temporarily discontinued. Ongoing, randomised patients were managed per Trial Protocol.	17 April 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sponsor decided to prematurely stop enrollment. This decision was based on the unfortunate inability to meet expected enrolment goals, a situation made far worse by the impact of the COVID-19 pandemic.