Clinical trial results:
A phase II randomised, double-blinded, placebo-controlled study to evaluate the efficacy, safety and tolerability of four orally administrated doses of BI 409306 during a 12-week treatment period in patients with schizophrenia on stable antipsychotic treatment.

Summary

EudraCT number	2013-005015-28
Trial protocol	DE
Global end of trial date	13 June 2016

Results information

Result version number	v1 (current)
This version publication date	28 June 2017
First version publication date	28 June 2017

Trial information

Trial identification

Sponsor protocol code	1289.6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02281773
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	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, 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	21 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 May 2016
Global end of trial reached?	Yes
Global end of trial date	13 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of trial is to investigate the efficacy, safety and tolerability of BI 409306 10, 25, 50 and 100 mg once daily compared to placebo given for 12 weeks in patients with schizophrenia on stable antipsychotic treatment. The study is designed to show superiority of BI 409306 over placebo in cognition and everyday living skills

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.

Background therapy:

Eligible patients must be on stable antipsychotic treatment prior to randomisation and the patients continued to receive the treatment throughout the duration of the trial as the background therapy.

Evidence for comparator: -

Actual start date of recruitment	10 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 44
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	United States: 532
Worldwide total number of subjects	697
EEA total number of subjects	29

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)	697
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A phase II multi-centre, multi-national, randomised, double-blind, placebo-controlled parallel group trial to evaluate the efficacy, safety and tolerability of four orally administrated doses of BI 409306 during a 12-week treatment period in patients with schizophrenia on stable antipsychotic treatment.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended a specialist site which ensured that they met all strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria were violated. 518 subjects were entered but 2 were not treated.

Period 1

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

Blinding implementation details:

This was double-blinded trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 409306 - 10 milligram

Arm description:

Subject received single oral dose of 10 milligram (mg) BI 409306 (film-coated tablet) along with two placebo matching 25mg/50mg tablets once daily for 12 weeks.

Arm type	Experimental
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:

Single oral dose of two placebo matching 25mg/50mg tablets once daily for 12 weeks

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:

Single oral dose of 10 milligram (mg) BI 409306 once daily for 12 weeks

Arm title	BI 409306 - 25 milligram

Arm description:

Subject received single oral dose of 25 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.

Arm type	Experimental

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:

Single oral dose of placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks

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:

Single oral dose of 25 milligram (mg) BI 409306 once daily for 12 weeks

Arm title	BI 409306 - 50 milligram

Arm description:

Subject received single oral dose of 50 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.

Arm type	Experimental
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:

Single oral dose of placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks

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:

Single oral dose of 50 milligram (mg) BI 409306 once daily for 12 weeks

Arm title	BI 409306 - 100 milligram

Arm description:

Subject received single oral dose of 100 milligram (mg) BI 409306 (2 film-coated tablets of 50 mg) along with placebo matching 10mg tablet once daily for 12 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:

Single oral dose of 100 milligram (mg) BI 409306 (2 film-coated tablets of 50 mg) once daily for 12 weeks

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:

Single oral dose of placebo matching 10mg tablet once daily for 12 weeks

Arm title	Placebo

Arm description:

Subject received single oral dose of placebo matching tablets (one placebo matching 10mg tablet and two placebo matching 25mg/50mg tablets) once daily for 12 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:

Single oral dose of placebo matching 10mg tablet and two placebo matching 25mg/50mg tablets once daily for 12 weeks

Number of subjects in period 1[1]	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram
Started	87	85	85
Completed	76	70	67
Not completed	11	15	18
Consent withdrawn by subject	2	8	6
Adverse event, non-fatal	6	1	4
Other Reason	-	4	2
Lost to follow-up	2	2	6
Protocol deviation	1	-	-

Number of subjects in period 1[1]	BI 409306 - 100 milligram	Placebo
Started	86	173
Completed	65	143
Not completed	21	30
Consent withdrawn by subject	6	8
Adverse event, non-fatal	8	9
Other Reason	3	1
Lost to follow-up	2	10
Protocol deviation	2	2

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: Baseline characteristics are based on the patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	BI 409306 - 10 milligram
Reporting group description:	
Subject received single oral dose of 10 milligram (mg) BI 409306 (film-coated tablet) along with two placebo matching 25mg/50mg tablets once daily for 12 weeks.	
Reporting group title	BI 409306 - 25 milligram
Reporting group description:	
Subject received single oral dose of 25 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.	
Reporting group title	BI 409306 - 50 milligram
Reporting group description:	
Subject received single oral dose of 50 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.	
Reporting group title	BI 409306 - 100 milligram
Reporting group description:	
Subject received single oral dose of 100 milligram (mg) BI 409306 (2 film-coated tablets of 50 mg) along with placebo matching 10mg tablet once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subject received single oral dose of placebo matching tablets (one placebo matching 10mg tablet and two placebo matching 25mg/50mg tablets) once daily for 12 weeks.	

Reporting group values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram
Number of subjects	87	85	85
Age categorical			
The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.			
Units: Subjects			

Age Continuous			
The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.			
Units: years			
arithmetic mean	44.1	43.2	41.4
standard deviation	± 8.9	± 9.4	± 9.5
Gender, Male/Female			
The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.			
Units: Subjects			
Female	34	29	20
Male	53	56	65

Reporting group values	BI 409306 - 100 milligram	Placebo	Total
Number of subjects	86	173	516
Age categorical			
The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.			
Units: Subjects			

Age Continuous			
The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.			
Units: years			
arithmetic mean	42.3	41.5	
standard deviation	± 9.5	± 9.7	-
Gender, Male/Female			
The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.			
Units: Subjects			
Female	28	45	156
Male	58	128	360

End points

End points reporting groups

Reporting group title	BI 409306 - 10 milligram
Reporting group description:	
Subject received single oral dose of 10 milligram (mg) BI 409306 (film-coated tablet) along with two placebo matching 25mg/50mg tablets once daily for 12 weeks.	
Reporting group title	BI 409306 - 25 milligram
Reporting group description:	
Subject received single oral dose of 25 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.	
Reporting group title	BI 409306 - 50 milligram
Reporting group description:	
Subject received single oral dose of 50 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.	
Reporting group title	BI 409306 - 100 milligram
Reporting group description:	
Subject received single oral dose of 100 milligram (mg) BI 409306 (2 film-coated tablets of 50 mg) along with placebo matching 10mg tablet once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subject received single oral dose of placebo matching tablets (one placebo matching 10mg tablet and two placebo matching 25mg/50mg tablets) once daily for 12 weeks.	

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

End point title	Change from baseline in the composite score of Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 12 weeks of treatment
End point description:	
Change from baseline in the composite score of Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) after 12 weeks of treatment. The trial was set up as "learn and confirm" model including 2 stages. Stage 1 analysis was conducted to identify the meaningful cognition endpoint(s) (CANTAB domain(s)) and the selected endpoint(s) were to be pre-specified as the primary endpoint(s) for Stage 2 analysis. Since none of the CANTAB outcome measures was selected in the Stage 1 analysis at planned time based on the pre-specified criteria, the MCCB composite score was chosen as the primary endpoint in the Stage 2 analysis, as pre-defined. The full analysis set (FAS) was to consist of all randomisation patients who were treated with at least one dose of study drug and had a baseline and at least one post baseline on treatment primary endpoint MCCB composite score.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79[1]	76[2]	69[3]	76[4]
Units: Unit on Scale				
least squares mean (standard error)	1.2 (± 0.71)	2.7 (± 0.74)	2.8 (± 0.75)	1.8 (± 0.73)

Notes:

[1] - Evaluable patients from FAS

[2] - Evaluable patients from FAS

[3] - Evaluable patients from FAS

[4] - Evaluable patients from FAS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	150[5]			
Units: Unit on Scale				
least squares mean (standard error)	2.5 (± 0.57)			

Notes:

[5] - Evaluable patients from FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM) was used with baseline value as fixed covariate and planned treatment, analysis visit, first test done, geographic region grouping 1, planned treatment by analysis visit and baseline value by analysis visit as fixed effects.

Comparison groups	BI 409306 - 10 milligram v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.1256 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.76
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.79

Notes:

[6] - Unstructured covariance structure has been used to fit the mixed model. Kenward−Roger was used to model degrees of freedom. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 10 mg minus Placebo.

[7] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM) was used with baseline value as fixed covariate and planned treatment, analysis visit, first test

done, geographic region grouping 1, planned treatment by analysis visit and baseline value by analysis visit as fixed effects.

Comparison groups	BI 409306 - 25 milligram v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.7337 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.84
Variability estimate	Standard error of the mean
Dispersion value	0.8

Notes:

[8] - Unstructured covariance structure has been used to fit the mixed model. Kenward−Roger was used to model degrees of freedom. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 25 mg minus Placebo.
[9] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

The restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM) was used with baseline value as fixed covariate and planned treatment, analysis visit, first test done, geographic region grouping 1, planned treatment by analysis visit and baseline value by analysis visit as fixed effects.

Comparison groups	BI 409306 - 50 milligram v Placebo
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.6994 [11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	1.95
Variability estimate	Standard error of the mean
Dispersion value	0.83

Notes:

[10] - Unstructured covariance structure has been used to fit the mixed model. Kenward−Roger was used to model degrees of freedom. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 50 mg minus Placebo.
[11] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

The restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM) was used with baseline value as fixed covariate and planned treatment, analysis visit, first test

done, geographic region grouping 1, planned treatment by analysis visit and baseline value by analysis visit as fixed effects.

Comparison groups	BI 409306 - 100 milligram v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.427 [13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	0.93
Variability estimate	Standard error of the mean
Dispersion value	0.79

Notes:

[12] - Unstructured covariance structure has been used to fit the mixed model. Kenward−Roger was used to model degrees of freedom. Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 100 mg minus Placebo.
[13] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Primary: Occurrence of serious adverse events (SAEs) (including the abnormalities of physical examination, vital signs, electrocardiogram (ECG) test and laboratory tests)

End point title	Occurrence of serious adverse events (SAEs) (including the abnormalities of physical examination, vital signs, electrocardiogram (ECG) test and laboratory tests)[14]

End point description:

Occurrence of serious adverse events (SAEs) (including the abnormalities of physical examination, vital signs, electrocardiogram (ECG) test and laboratory tests). The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to 20 weeks

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87[15]	85[16]	85[17]	86[18]
Units: Percentage of Participants				
number (not applicable)	0	0	0	0

Notes:

[15] - TS

[16] - TS

[17] - TS

[18] - TS

End point values	Placebo			

Subject group type	Reporting group			
Number of subjects analysed	173[19]			
Units: Percentage of Participants				
number (not applicable)	5.8			

Notes:

[19] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of Protocol-specified adverse events of special interest (AESI)

End point title	Occurrence of Protocol-specified adverse events of special interest (AESI)[20]

End point description:

Occurrence of Protocol-specified adverse events of special interest (AESI). The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to 20 weeks

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87[21]	85[22]	85[23]	86[24]
Units: Percentage of Participants				
number (not applicable)	0	0	0	0

Notes:

[21] - TS

[22] - TS

[23] - TS

[24] - TS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	173[25]			
Units: Percentage of Participants				
number (not applicable)	0			

Notes:

[25] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Dramatic worsening of disease state as assessed by Positive and Negative Syndrome Scale (PANSS)

End point title	Dramatic worsening of disease state as assessed by Positive

	and Negative Syndrome Scale (PANSS)[26]

End point description:

Dramatic worsening of disease state as assessed by Positive and Negative Syndrome Scale (PANSS). The descriptive statistics of change from baseline (CFB) PANSS score at week 6 and week 12 are presented. The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.

End point type	Primary

End point timeframe:

Baseline, Week 6 and Week 12

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87[27]	85[28]	85[29]	86[30]
Units: Unit on Scale				
arithmetic mean (standard deviation)				
CFB at Week 6 (N= 79, 74, 67, 71, 154)	-0.68 (± 6.022)	-0.28 (± 4.507)	-1.09 (± 5.415)	-1.2 (± 5.426)
CFB at Week 12 (N= 83, 78, 76, 81, 157)	-2.59 (± 5.342)	-0.97 (± 5.42)	-1.58 (± 6.99)	-0.94 (± 6.315)

Notes:

[27] - TS

[28] - TS

[29] - TS

[30] - TS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	173[31]			
Units: Unit on Scale				
arithmetic mean (standard deviation)				
CFB at Week 6 (N= 79, 74, 67, 71, 154)	-1.81 (± 5.895)			
CFB at Week 12 (N= 83, 78, 76, 81, 157)	-1.66 (± 6.942)			

Notes:

[31] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Suicidality as assessed by Columbia Suicidal Severity Rating Scale (C-SSRS)

End point title	Suicidality as assessed by Columbia Suicidal Severity Rating Scale (C-SSRS)[32]

End point description:

Suicidality as assessed by Columbia Suicidal Severity Rating Scale (C-SSRS). The number (%) of subjects with an event of Suicidal Ideation (Wish to be dead, Non−specific active suicidal thoughts, Active suicidal ideation with any methods (not plan) without intent to act, Active suicidal ideation with some intent to act without specific plan, Active suicidal ideation with specific plan and intent) or Suicidal

Behavior (Preparatory acts or behavior, Aborted attempt, Interrupted attempt, Non−fatal suicide attempt, Completed suicide) or Self−injurious behavior without suicidal intent is presented. The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug (Number of subjects with a post baseline C−SSRS).

End point type	Primary

End point timeframe:

Up to 12 weeks

Notes:

[32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84[33]	84[34]	79[35]	85[36]
Units: Percentage of Participants				
number (not applicable)	0	1.2	2.5	1.2

Notes:

[33] - TS

[34] - TS

[35] - TS

[36] - TS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	166[37]			
Units: Percentage of Participants				
number (not applicable)	3.6			

Notes:

[37] - TS

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) global ratings after 12 weeks of treatment

End point title	Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) global ratings after 12 weeks of treatment

End point description:

Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) global ratings after 12 weeks of treatment. SCoRS is a 20-item interview-based assessment of cognitive deficits and the degree to which they affect day-to-day functions. Each item was rated on a 4-point scale. Higher ratings reflected a greater degree of impairment. The composite score is the sum of the non-missing response. If any individual item was missing, it was imputed with the average of that patient's non- missing responses. If >5 items were missing, the total score was missing. The full analysis set (FAS) was to consist of all randomisation patients who were treated with at least one dose of study drug and had a baseline and at least one post baseline on treatment primary endpoint MCCB composite score.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[38]	75[39]	73[40]	80[41]
Units: Unit on Scale				
least squares mean (standard error)	-2.2 (± 0.53)	-3.1 (± 0.56)	-2 (± 0.56)	-2.3 (± 0.54)

Notes:

[38] - Evaluable patients from FAS

[39] - Evaluable patients from FAS

[40] - Evaluable patients from FAS

[41] - Evaluable patients from FAS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	156[42]			
Units: Unit on Scale				
least squares mean (standard error)	-2.5 (± 0.39)			

Notes:

[42] - Evaluable patients from FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 10 milligram v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.5972 [44]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[43] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 10 mg minus Placebo.

[44] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

	Statistical analysis 2

Statistical analysis title	

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 25 milligram v Placebo
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.3817 [46]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.68

Notes:

[45] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 25 mg minus Placebo.
[46] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 50 milligram v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.48 [48]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.68

Notes:

[47] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 50 mg minus Placebo.
[48] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 100 milligram v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.7507 [50]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[49] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 100 mg minus Placebo.
[50] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Secondary: Change from baseline in Clinical Global Impressions-Severity (CGI-S) scale score after 12 weeks of treatment

End point title	Change from baseline in Clinical Global Impressions-Severity (CGI-S) scale score after 12 weeks of treatment

End point description:

Change from baseline in Clinical Global Impressions-Severity (CGI-S) scale score after 12 weeks of treatment. The CGI-S is a one-item evaluation completed by the clinician on the patient's severity of psychopathology. The CGI-S was rated ordinally from one to 7. The full analysis set (FAS) was to consist of all randomisation patients who were treated with at least one dose of study drug and had a baseline and at least one post baseline on treatment primary endpoint MCCB composite score.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[51]	77[52]	73[53]	81[54]
Units: Unit on Scale				
least squares mean (standard error)	-0.1 (± 0.05)	-0.1 (± 0.05)	-0.1 (± 0.05)	-0.1 (± 0.05)

Notes:

[51] - Evaluable patients from FAS

[52] - Evaluable patients from FAS

[53] - Evaluable patients from FAS

[54] - Evaluable patients from FAS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	157[55]			
Units: Unit on Scale				
least squares mean (standard error)	-0.1 (± 0.03)			

Notes:

[55] - Evaluable patients from FAS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 10 milligram v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	= 0.9399 [57]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[56] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 10 mg minus Placebo.

[57] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 25 milligram v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	= 0.9919 [59]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[58] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 25 mg minus Placebo.
[59] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 50 milligram v Placebo
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other[60]
P-value	= 0.3027 [61]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[60] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 50 mg minus Placebo.
[61] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analyses of covariance (ANCOVA) were used to assess between−group differences (BI 409306 group minus placebo group) in the modelled changes from baseline to Week 12. The dependent variable was the change from the baseline score at Week 12 during the treatment period adjusted for fixed categorical covariates of treatment as well as fixed continuous covariates of baseline score.

Comparison groups	BI 409306 - 100 milligram v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	other[62]
P-value	= 0.3901 [63]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[62] - Mean Difference (Final Values) is actually the Adjusted mean difference calculated as BI 409306 100 mg minus Placebo.
[63] - Due to the exploratory nature of this trial, no multiplicity adjustment was made. All statistical testing was performed using a two-sided, α=0.05 level of significance.

Secondary: Patient Global Impressions-Improvement (PGI-I) scale score measured after 12 weeks of treatment

End point title	Patient Global Impressions-Improvement (PGI-I) scale score measured after 12 weeks of treatment

End point description:

Patient Global Impressions-Improvement (PGI-I) scale score measured after 12 weeks of treatment. The PGI of improvement is a simple evaluation completed by the patient to assess the patient's overall evaluation of his/her status. The PGI of improvement was rated ordinally from one to 7. The full analysis set (FAS) was to consist of all randomisation patients who were treated with at least one dose of study drug and had a baseline and at least one post baseline on treatment primary endpoint MCCB composite score.

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[64]	77[65]	73[66]	82[67]
Units: Unit on Scale				
arithmetic mean (standard deviation)	2.988 (± 1.117)	2.883 (± 1.124)	3.192 (± 1.101)	3.049 (± 1.342)

Notes:

[64] - Evaluable patients from FAS

[65] - Evaluable patients from FAS

[66] - Evaluable patients from FAS

[67] - Evaluable patients from FAS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	157[68]			
Units: Unit on Scale				
arithmetic mean (standard deviation)	3.038 (± 1.109)			

Notes:

[68] - Evaluable patients from FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in PANSS negative symptom factor score after 12 weeks of treatment (for subset of patients diagnosed with negative symptom)

End point title	Change from baseline in PANSS negative symptom factor score after 12 weeks of treatment (for subset of patients diagnosed with negative symptom)

End point description:

Change from baseline in PANSS negative symptom factor score after 12 weeks of treatment (for subset of patients diagnosed with negative symptom). This outcome measure was not analysed due to low number of patients in the PANSS negative symptom subgroup. The PANSS negative symptom scale has 7 items. Each was rated from one to 7 points. The total factor score was the summation of the 7 points for each item, leading the total score ranging from 7 to 49.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[69]	0[70]	0[71]	0[72]
Units: NA				
number (not applicable)				

Notes:

[69] - Not analysed due to low number of patients in the PANSS negative symptom subgroup.

[70] - Not analysed due to low number of patients in the PANSS negative symptom subgroup.

[71] - Not analysed due to low number of patients in the PANSS negative symptom subgroup.

[72] - Not analysed due to low number of patients in the PANSS negative symptom subgroup.

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[73]			
Units: NA				
number (not applicable)				

Notes:

[73] - Not analysed due to low number of patients in the PANSS negative symptom subgroup.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in psychopathology symptoms as assessed by Positive and Negative Syndrome Scale (PANSS)

End point title	Change in psychopathology symptoms as assessed by Positive and Negative Syndrome Scale (PANSS)

End point description:

Change in psychopathology symptoms as assessed by Positive and Negative Syndrome Scale (PANSS). The descriptive statistics of change from baseline (CFB) PANSS score at week 6 and week 12 are presented. The treated set (TS) was to consist of all patients who were randomised and treated with at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 6 and Week 12

End point values	BI 409306 - 10 milligram	BI 409306 - 25 milligram	BI 409306 - 50 milligram	BI 409306 - 100 milligram
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87[74]	85[75]	85[76]	86[77]
Units: Unit on Scale				
arithmetic mean (standard deviation)				
CFB at Week 6 (N= 79, 74, 67, 71, 154)	-0.39 (± 3.677)	-0.22 (± 3.262)	-0.31 (± 3.759)	-0.79 (± 3.497)
CFB at Week 12 (N= 83, 78, 76, 81, 157)	-1.36 (± 3.039)	-0.79 (± 3.277)	-0.68 (± 4.253)	-0.38 (± 3.587)

Notes:

[74] - TS

[75] - TS

[76] - TS

[77] - TS

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	173[78]			
Units: Unit on Scale				
arithmetic mean (standard deviation)				
CFB at Week 6 (N= 79, 74, 67, 71, 154)	-0.99 (± 3.954)			
CFB at Week 12 (N= 83, 78, 76, 81, 157)	-0.76 (± 4.007)			

Notes:

[78] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first drug administration until 4 weeks after the last drug administration, up to 16 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	BI 409306 - 25 milligram
Reporting group description:	
Subject received single oral dose of 25 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.	
Reporting group title	BI 409306 - 10 milligram
Reporting group description:	
Subject received single oral dose of 10 milligram (mg) BI 409306 (film-coated tablet) along with two placebo matching 25mg/50mg tablets once daily for 12 weeks.	
Reporting group title	BI 409306 - 100 milligram
Reporting group description:	
Subject received single oral dose of 100 milligram (mg) BI 409306 (2 film-coated tablets of 50 mg) along with placebo matching 10mg tablet once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subject received single oral dose of placebo matching tablets (one placebo matching 10mg tablet and two placebo matching 25mg/50mg tablets) once daily for 12 weeks.	
Reporting group title	BI 409306 - 50 milligram
Reporting group description:	
Subject received single oral dose of 50 milligram (mg) BI 409306 (film-coated tablet) along with placebo matching 10mg and 25mg/50mg tablet once daily for 12 weeks.	

Serious adverse events	BI 409306 - 25 milligram	BI 409306 - 10 milligram	BI 409306 - 100 milligram
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Empyema			
subjects affected / exposed	0 / 85 (0.00%)	0 / 87 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo	BI 409306 - 50 milligram	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 173 (5.78%)	0 / 85 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertensive crisis			

subjects affected / exposed	1 / 173 (0.58%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 173 (0.58%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 173 (0.58%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 173 (0.58%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	5 / 173 (2.89%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	3 / 173 (1.73%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Empyema			
subjects affected / exposed	1 / 173 (0.58%)	0 / 85 (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 - 25 milligram	BI 409306 - 10 milligram	BI 409306 - 100 milligram
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 85 (10.59%)	5 / 87 (5.75%)	12 / 86 (13.95%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 85 (5.88%)	5 / 87 (5.75%)	1 / 86 (1.16%)
occurrences (all)	7	5	1
Eye disorders			
Photophobia			
subjects affected / exposed	2 / 85 (2.35%)	0 / 87 (0.00%)	6 / 86 (6.98%)
occurrences (all)	2	0	6
Visual brightness			
subjects affected / exposed	2 / 85 (2.35%)	0 / 87 (0.00%)	6 / 86 (6.98%)
occurrences (all)	2	0	6

Non-serious adverse events	Placebo	BI 409306 - 50 milligram	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 173 (6.94%)	9 / 85 (10.59%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 173 (5.78%)	4 / 85 (4.71%)	
occurrences (all)	14	4	
Eye disorders			
Photophobia			
subjects affected / exposed	2 / 173 (1.16%)	2 / 85 (2.35%)	
occurrences (all)	2	3	
Visual brightness			
subjects affected / exposed	0 / 173 (0.00%)	3 / 85 (3.53%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2014	Protocol amendment 1 was implemented before first patient was enrolled. The major changes were: Removal of body temperature measurement from the vital sign examinations as BI 409306 rarely interfered with temperature regulation and there is no fatal or lifethreatening change in body temperature caused by BI 409306, according to the preclinical and clinical data to date. Addition of a window to allow more flexibility for the ECG testing. To provide updated fasting instructions for blood sampling in this study in order to align with the fasting requirement of BI 409306 administration. To clarify the unblinding procedure for Stage 1 analysis. The unblinded results of Stage 1 were to be reviewed only by the trial and project team, including TAH, TMM, TCM, SEG member for CNS, PSTAT, TSTAT, and TPROG.
28 October 2014	Protocol amendment 2 was implemented before first patient was enrolled. The major changes were: Setting additional restrictions for the current antipsychotic and concomitant psychotropic medications in order to minimize the effect on the cognitive function caused by the patient's current treatment. Adding C-SSRS assessment to Visit 3, Visit 5 and Follow-up Visit to align with the FDA's suggestion and FDA guidance: "Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (August, 2012)". Adding new exclusion criterion to exclude patients who needed to take strong or moderate CYP3A4 inhibitors because CYP3A4 inhibitors potentially might increase exposure to BI 409306 in CYP2C19 Poor Metabolizers (PM) based on the up-to-date clinical trial data. Adding new requirement to exclusion criterion number 16 to exclude patients who received any cognitive-enhancing therapy or procedure recently because the patient's cognitive impairment severity might be changed by receiving this kind of therapy or procedure. Adding additional requirements and instructions to the prohibited concomitant treatment section to avoid the drug-drug interaction and the possible effect on the patient's cognitive function caused by those medications and to avoid the drug-drug interaction. Revising the (S)AE reporting instruction of vision-related AEs according to FDA's comment. Revising Japan specific safety reporting instruction in Section 5.2.2.2. Removing the Visit 2 final PK blood sampling time point to shorten the length of PK blood sampling time schedule in order to reduce the burden of complying with study procedures. Revising the wordings of CANTAB domain selection criteria to clarify the criteria which were to be used as a guide for CANTAB domain selection. Updating the instruction and procedures of DILI case follow-up in order to align with the updated DILI Checklist.
09 September 2015	Protocol amendment 3 was implemented after study initiation. The major changes were: To update recruitment plan for Japan based on the local regulatory requirement and to add the interim analysis plan. To add criterion 1b-4 to clarify the washout period for anticholinergics, antiepileptics and lithium. To update the fasting requirement of the study drug administration. Patients were instructed to take the study drug orally with water in the morning at approximately the same time every day with or without food. To correct, update and clarify statistical methods which will be used for data analysis. To update the unblinding procedures for pharmacokinetic data analysis, thus to allow the bioanalytical group to perform some appropriate pharmacokinetic analytical determination (e.g. exclusion from the analyses of pharmacokinetic samples taken from placebo patients). To update the instruction of suicidality assessment and AEs/SAEs reporting rule, thus to align with the FDA guidance on prospective assessment of suicidal ideation and behavior.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

An outcome measure "Change from baseline in PANSS negative symptom factor score after 12 weeks of treatment" was not analysed due to low number of patients in the PANSS negative symptom subgroup.

Notes: