Clinical trial results:
A phase II randomized, double-blinded, placebo-controlled, parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia

Summary

EudraCT number	2016-000285-28
Trial protocol	DE AT ES IT
Global end of trial date	29 January 2020

Results information

Result version number	v1
This version publication date	12 February 2021
First version publication date	12 February 2021

Trial information

Trial identification

Sponsor protocol code	1346.9

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02832037
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	27 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2019
Global end of trial reached?	Yes
Global end of trial date	29 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this trial were to provide proof of clinical concept (PoCC) and dose finding data in patients with schizophrenia on stable antipsychotic treatment who were treated with oral once daily administration of BI 425809 or placebo.

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	13 September 2016
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	Austria: 2
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Poland: 75
Country: Number of subjects enrolled	Korea, Republic of: 57
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Taiwan: 29
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 320
Worldwide total number of subjects	684
EEA total number of subjects	170

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)	684
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A phase II randomized, double-blind, double-dummy, placebo-controlled, multi-center, multi-national, parallel-group trial. Abbreviation: FAS=All subjects randomized, treated with at least 1 dose of trial drug, a non-missing baseline measurement (mt) and at least 1 non-missing post-baseline and on-treatment mt for the primary or secondary endpoint.

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. The number of subjects reported to start in the baseline period are actually the randomized subjects.

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 425809 2 mg once a day (q.d.)

Arm description:

2 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 1 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm type	Experimental
Investigational medicinal product name	BI 425809 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 1 mg BI 425809) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm title	BI 425809 5 mg q.d.

Arm description:

5 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 5 mg BI 425809, 1 placebo tablet matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm type	Experimental
Investigational medicinal product name	BI 425809 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 5 mg BI 425809) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm title	BI 425809 10 mg q.d.

Arm description:

10 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 5 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food in the morning, once daily. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm type	Experimental
Investigational medicinal product name	BI 425809 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 5 mg BI 425809) with water, with or without food in the morning, once daily. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm title	BI 425809 25 mg q.d.

Arm description:

25 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 25 mg BI 425809, 2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm type	Experimental
Investigational medicinal product name	BI 425809 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 25 mg BI 425809) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Arm title	Placebo q.d.

Arm description:

Placebo administered orally (2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

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:

Placebo administered orally (2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Number of subjects in period 1[1]	BI 425809 2 mg once a day (q.d.)	BI 425809 5 mg q.d.	BI 425809 10 mg q.d.
Started	85	84	85
Completed	66	72	77
Not completed	19	12	8
Consent withdrawn by subject	9	8	-
Adverse event, non-fatal	5	4	-
Administrative reasons	-	-	1
Lost to follow-up	2	-	3
Protocol deviation	3	-	4

Number of subjects in period 1[1]	BI 425809 25 mg q.d.	Placebo q.d.
Started	85	170
Completed	78	151
Not completed	7	19
Consent withdrawn by subject	4	8
Adverse event, non-fatal	2	4
Administrative reasons	-	-
Lost to follow-up	-	5
Protocol deviation	1	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: The number of subjects reported to start in the baseline period are actually the randomized subjects.

Baseline characteristics

Reporting groups	
Reporting group title	BI 425809 2 mg once a day (q.d.)
Reporting group description:	
2 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 1 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	BI 425809 5 mg q.d.
Reporting group description:	
5 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 5 mg BI 425809, 1 placebo tablet matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	BI 425809 10 mg q.d.
Reporting group description:	
10 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 5 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food in the morning, once daily. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	BI 425809 25 mg q.d.
Reporting group description:	
25 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 25 mg BI 425809, 2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	Placebo q.d.
Reporting group description:	
Placebo administered orally (2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	

Reporting group values	BI 425809 2 mg once a day (q.d.)	BI 425809 5 mg q.d.	BI 425809 10 mg q.d.
Number of subjects	85	84	85
Age categorical			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	85	84	85
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
The Treated Set included all participants who were randomized and were treated with at least 1 dose of trial medication.			
Units: years			
arithmetic mean	36.5	37.5	37.9
standard deviation	± 8.5	± 7.9	± 6.8

Sex: Female, Male			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Participants			
Female	34	27	24
Male	51	57	61
Ethnicity (NIH/OMB)			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Subjects			
Hispanic or Latino	6	8	7
Not Hispanic or Latino	79	76	78
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	24	18	25
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	15	20	21
White	44	44	39
More than one race	2	1	0
Unknown or Not Reported	0	0	0
MATRICS Consensus Cognitive Battery (MCCB) overall composite t-score			
Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) overall composite t-score was derived from scores of seven cognitive domains (Speed of Processing, Verbal Learning, Working Memory, Reasoning and Problem Solving, Visual Learning, Social Cognition, Attention/Vigilance) obtained from a total of ten tests. MCCB overall composite t-score ranges typically between −20 and +99 where a larger MCCB overall composite t-score indicates better cognition. Treated Set: All subjects randomized and treated with at least 1 dose of trial drug.			
Units: Score on a scale			
arithmetic mean	30.0	32.8	31.8
standard deviation	± 13.8	± 12.0	± 12.8

Reporting group values	BI 425809 25 mg q.d.	Placebo q.d.	Total
Number of subjects	85	170	509
Age categorical			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	85	170	509
From 65-84 years	0	0	0
85 years and over	0	0	0

Age Continuous			
The Treated Set included all participants who were randomized and were treated with at least 1 dose of trial medication.			
Units: years			
arithmetic mean	36.2	37.2	
standard deviation	± 7.8	± 7.7	-
Sex: Female, Male			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Participants			
Female	35	60	180
Male	50	110	329
Ethnicity (NIH/OMB)			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Subjects			
Hispanic or Latino	5	15	41
Not Hispanic or Latino	80	155	468
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.			
Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	22	56	145
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	22	41	119
White	38	72	237
More than one race	2	1	6
Unknown or Not Reported	0	0	0
MATRICS Consensus Cognitive Battery (MCCB) overall composite t-score			
Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) overall composite t-score was derived from scores of seven cognitive domains (Speed of Processing, Verbal Learning, Working Memory, Reasoning and Problem Solving, Visual Learning, Social Cognition, Attention/Vigilance) obtained from a total of ten tests. MCCB overall composite t-score ranges typically between –20 and +99 where a larger MCCB overall composite t-score indicates better cognition. Treated Set: All subjects randomized and treated with at least 1 dose of trial drug.			
Units: Score on a scale			
arithmetic mean	30.2	32.3	
standard deviation	± 13.2	± 13.6	-

End points

End points reporting groups

Reporting group title	BI 425809 2 mg once a day (q.d.)
Reporting group description:	
2 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 1 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	BI 425809 5 mg q.d.
Reporting group description:	
5 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 5 mg BI 425809, 1 placebo tablet matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	BI 425809 10 mg q.d.
Reporting group description:	
10 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 5 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food in the morning, once daily. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	BI 425809 25 mg q.d.
Reporting group description:	
25 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 25 mg BI 425809, 2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	
Reporting group title	Placebo q.d.
Reporting group description:	
Placebo administered orally (2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).	

Primary: Change from baseline in cognitive function as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) overall composite t-score after 12 weeks of treatment

End point title	Change from baseline in cognitive function as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) overall composite t-score after 12 weeks of treatment
End point description:	
MCCB overall composite t-score was derived from scores of seven cognitive domains (Speed of Processing, Verbal Learning, Working Memory, Reasoning and Problem Solving, Visual Learning, Social Cognition, Attention/Vigilance) obtained from a total of ten tests (Trail Making Test, Brief Assessment of Cognition in Schizophrenia: symbol coding subtest, Hopkins Verbal Learning Test, Wechsler Memory Scale test: Spatial Span subtest, Letter-Number Span test, Neuropsychological Assessment Battery: mazes subtest, Brief Visuospatial Memory Test, Category Fluency test: animal naming, Mayer-Salovey-Caruso Emotional Intelligence Test: managing emotions branch, Continuous Performance Test). MCCB overall composite t-score ranges typically between –20 and +99, where a larger MCCB overall composite t-score indicates better cognition. Mixed-effects Model Repeated Measures (MMRM) was fitted to calculate adjusted mean, standard error, MMRM details in Statistical Analysis section.	
End point type	Primary
End point timeframe:	
Baseline, after 6 and 12 weeks of treatment	

End point values	BI 425809 2 mg once a day (q.d.)	BI 425809 5 mg q.d.	BI 425809 10 mg q.d.	BI 425809 25 mg q.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79[1]	80[2]	82[3]	83[4]
Units: units on a scale				
least squares mean (standard error)	1.784 (± 0.6805)	1.641 (± 0.6656)	3.486 (± 0.6410)	3.234 (± 0.6410)

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

End point values	Placebo q.d.			
Subject group type	Reporting group			
Number of subjects analysed	163[5]			
Units: units on a scale				
least squares mean (standard error)	1.504 (± 0.4579)			

Notes:

[5] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, linear in log, Emax, Sigmoid Emax, logistic, and beta) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0145 [6]
Method	MCP-Mod linear model fit

Notes:

[6] - Adjusted for multiplicity.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, linear in log, Emax, Sigmoid Emax, logistic, and beta) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0148 [7]
Method	MCP-Mod linear in log model fit

Notes:

[7] - Adjusted for multiplicity.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Emax model assumption: 20% of the maximum effect is achieved at 2 mg of BI 425809.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0089 [8]
Method	MCP-Mod Emax model fit

Notes:

[8] - Adjusted for multiplicity.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Sigmoid Emax model assumption: 25% of the maximum effect is achieved at 5 mg and 75% of the maximum effect is achieved at 10 mg of BI 425809.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0038 [9]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[9] - Adjusted for multiplicity.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Logistic model assumption: 10% of the maximum effect is achieved at 5 mg and 50% of the maximum effect is achieved at 10 mg of BI 425809.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0085 [10]
Method	MCP-Mod logistic model fit

Notes:

[10] - Adjusted for multiplicity.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Beta model assumption: 75% of maximum (max) effect at 2 mg, 87.5% of max effect at 5 mg, 25% of max effect at 25 mg, max effect at 10 mg BI 425809, scalar parameter=26.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.228 [11]
Method	MCP-Mod beta model fit

Notes:

[11] - Adjusted for multiplicity.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Mixed Model Repeated Measures (MMRM) included fixed, categorical factors of treatment, analysis visit as repeated measures per subject, and treatment by analysis visit interaction, continuous fixed covariate of baseline value and baseline value by analysis visit interaction, subject as random effect, covariance structure= Unstructured.

Comparison groups	BI 425809 2 mg once a day (q.d.) v Placebo q.d.
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	≤ 0.733 [13]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.332
upper limit	1.892
Variability estimate	Standard error of the mean
Dispersion value	0.8205

Notes:

[12] - Kenward-Roger was used to estimate denominator degrees of freedom. Difference of adjusted means based on MMRM was calculated as BI 425809 - placebo.
[13] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Mixed Model Repeated Measures (MMRM) included fixed, categorical factors of treatment, analysis visit as repeated measures per subject, and treatment by analysis visit interaction, continuous fixed covariate of baseline value and baseline value by analysis visit interaction, subject as random effect, covariance structure= Unstructured.

Comparison groups	BI 425809 5 mg q.d. v Placebo q.d.
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.8655 [14]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	0.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	1.724
Variability estimate	Standard error of the mean
Dispersion value	0.8074

Notes:

[14] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Mixed Model Repeated Measures (MMRM) included fixed, categorical factors of treatment, analysis visit as repeated measures per subject, and treatment by analysis visit interaction, continuous fixed covariate of baseline value and baseline value by analysis visit interaction, subject as random effect, covariance structure= Unstructured.

Comparison groups	BI 425809 10 mg q.d. v Placebo q.d.
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0122 [15]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	1.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.434
upper limit	3.53
Variability estimate	Standard error of the mean
Dispersion value	0.7875

Notes:

[15] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Mixed Model Repeated Measures (MMRM) included fixed, categorical factors of treatment, analysis visit

as repeated measures per subject, and treatment by analysis visit interaction, continuous fixed covariate of baseline value and baseline value by analysis visit interaction, subject as random effect, covariance structure= Unstructured.

Comparison groups	BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0287 [16]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.181
upper limit	3.28
Variability estimate	Standard error of the mean
Dispersion value	0.7884

Notes:

[16] - P-value is considered nominal.

Secondary: Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 12 weeks of treatment

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

End point description:

SCoRS total score was derived as the sum of non-missing responses from 20 interview-based items rated by an interviewer on a 4-point scale. A response of "not available" to an item was treated as missing. If six or more of the 20 items were missing for a participant at a visit, then the corresponding SCoRS total score was missing for that participant at the visit. If five or less of the 20 items were missing for a participant at a visit, then the item(s) with missing value(s) were imputed first with the average of the non-missing item values, then the SCoRS total score for the participant at the visit was derived as the sum of non-missing item values and the imputed item values. SCoRS total score is between 20 and 80 where higher score values represent greater degree of impairment in day-to-day functions due to cognitive deficits.
Analysis of covariance model was fitted to calculate adjusted mean and standard error, model details in the Statistical Analysis section.

End point type	Secondary

End point timeframe:

Baseline and after 12 weeks of treatment

End point values	BI 425809 2 mg once a day (q.d.)	BI 425809 5 mg q.d.	BI 425809 10 mg q.d.	BI 425809 25 mg q.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	77[17]	80[18]	82[19]	83[20]
Units: units on a scale				
least squares mean (standard error)	-1.637 (± 0.5992)	-3.652 (± 0.5890)	-3.078 (± 0.5803)	-3.887 (± 0.5770)

Notes:

[17] - FAS

[18] - FAS

[19] - FAS

[20] - FAS

End point values	Placebo q.d.			
Subject group type	Reporting group			
Number of subjects analysed	158[21]			
Units: units on a scale				
least squares mean (standard error)	-2.815 (± 0.4181)			

Notes:

[21] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, linear in log, Emax, Sigmoid Emax, logistic, and beta) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.066 [22]
Method	MCP-Mod linear model fit

Notes:

[22] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, linear in log, Emax, Sigmoid Emax, logistic, and beta) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.1619 [23]
Method	MCP-Mod linear in log model fit

Notes:

[23] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response

patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Emax model assumption: 20% of the maximum effect is achieved at 2 mg of BI 425809.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0832 [24]
Method	MCP-Mod Emax model fit

Notes:

[24] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Sigmoid Emax model assumption: 25% of the maximum effect is achieved at 5 mg and 75% of the maximum effect is achieved at 10 mg of BI 425809.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0625 [25]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[25] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Logistic model assumption: 10% of the maximum effect is achieved at 5 mg and 50% of the maximum effect is achieved at 10 mg of BI 425809.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0768 [26]
Method	MCP-Mod logistic model fit

Notes:

[26] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 425809 and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns while protecting the overall probability of type I error (one-sided alpha of 0.05). Beta model assumption: 75% of maximum (max) effect at 2 mg, 87.5% of max effect at 5 mg, 25% of max effect at 25 mg, max effect at 10 mg BI 425809, scalar parameter=26.

Comparison groups	BI 425809 2 mg once a day (q.d.) v BI 425809 5 mg q.d. v BI 425809 10 mg q.d. v BI 425809 25 mg q.d. v Placebo q.d.

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.7479 [27]
Method	MCP-Mod beta model fit

Notes:

[27] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Analysis of covariance (ANCOVA) model included treatment as fixed categorical factor, and baseline score as continuous fixed covariate.

Comparison groups	BI 425809 2 mg once a day (q.d.) v Placebo q.d.
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.11 [28]
Method	ANCOVA
Parameter estimate	Difference of adjusted means
Point estimate	1.178
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.258
upper limit	2.613
Variability estimate	Standard error of the mean
Dispersion value	0.7306

Notes:

[28] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Analysis of covariance (ANCOVA) model included treatment as fixed categorical factor, and baseline score as continuous fixed covariate.

Comparison groups	BI 425809 5 mg q.d. v Placebo q.d.
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.25 [29]
Method	ANCOVA
Parameter estimate	Difference of adjusted means
Point estimate	-0.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.257
upper limit	0.582
Variability estimate	Standard error of the mean
Dispersion value	0.7224

Notes:

[29] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Analysis of covariance (ANCOVA) model included treatment as fixed categorical factor, and baseline score as continuous fixed covariate.

Comparison groups	BI 425809 10 mg q.d. v Placebo q.d.
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.71 [30]
Method	ANCOVA
Parameter estimate	Difference of adjusted means
Point estimate	-0.263
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.669
upper limit	1.142
Variability estimate	Standard error of the mean
Dispersion value	0.7152

Notes:

[30] - P-value is considered nominal.

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Secondary analysis. No formal hypotheses were tested.
Analysis of covariance (ANCOVA) model included treatment as fixed categorical factor, and baseline score as continuous fixed covariate.

Comparison groups	BI 425809 25 mg q.d. v Placebo q.d.
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.13 [31]
Method	ANCOVA
Parameter estimate	Difference of adjusted means
Point estimate	-1.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.473
upper limit	0.328
Variability estimate	Standard error of the mean
Dispersion value	0.7125

Notes:

[31] - P-value is considered nominal.

Secondary: Percentage of participants with Adverse Events

End point title	Percentage of participants with Adverse Events

End point description:

Percentage of participants with Adverse Events.
The Treated Set (TS) included all subjects who were randomized and were treated with at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

On-treatment period, that is, from first intake of any trial drug until the last intake of any trial drug (planned: 84 days) + residual effect period (11 days), up to 103 days

End point values	BI 425809 2 mg once a day (q.d.)	BI 425809 5 mg q.d.	BI 425809 10 mg q.d.	BI 425809 25 mg q.d.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	85[32]	84[33]	85[34]	85[35]
Units: Percentage of participants				
number (not applicable)	58.8	52.4	41.2	42.4

Notes:

[32] - TS

[33] - TS

[34] - TS

[35] - TS

End point values	Placebo q.d.			
Subject group type	Reporting group			
Number of subjects analysed	170[36]			
Units: Percentage of participants				
number (not applicable)	43.5			

Notes:

[36] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For Serious and Other Adverse Events: On-treatment period, that is, from first intake of any trial drug until the last intake of any trial drug (planned: 84 days) + residual effect period (11 days), up to 103 days.

Adverse event reporting additional description:

Timeframe for "Deaths (all causes)": On-treatment period + Follow-up period (planned: 28±7 days), up to 127 days.
The Treated Set included all subjects who were randomized and were treated with at least 1 dose of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	BI 425809 2mg QD

Reporting group description:

2 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 1 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Reporting group title	BI 425809 5mg QD

Reporting group description:

5 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 5 mg BI 425809, 1 placebo tablet matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Reporting group title	BI 425809 10mg QD

Reporting group description:

10 milligram (mg) of BI 425809 administered orally (2 tablets with tablet strength 5 mg BI 425809, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food in the morning, once daily. Continuous daily dosing for 12 weeks (planned treatment duration).

Reporting group title	BI 425809 25mg QD

Reporting group description:

25 milligram (mg) of BI 425809 administered orally (1 tablet with tablet strength 25 mg BI 425809, 2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Reporting group title	Placebo QD

Reporting group description:

Placebo administered orally (2 placebo tablets matching 1 mg and 5 mg BI 425809 tablets, 1 placebo tablet matching 25 mg BI 425809 tablets) with water, with or without food, once daily in the morning. Continuous daily dosing for 12 weeks (planned treatment duration).

Serious adverse events	BI 425809 2mg QD	BI 425809 5mg QD	BI 425809 10mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 85 (2.35%)	4 / 84 (4.76%)	2 / 85 (2.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 85 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 85 (0.00%)	0 / 84 (0.00%)	0 / 85 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 85 (0.00%)	0 / 84 (0.00%)	0 / 85 (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
Radius fracture			
subjects affected / exposed	0 / 85 (0.00%)	0 / 84 (0.00%)	0 / 85 (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			
Drug dependence			
subjects affected / exposed	0 / 85 (0.00%)	0 / 84 (0.00%)	0 / 85 (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
Fear of disease			
subjects affected / exposed	0 / 85 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 85 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic symptom			

subjects affected / exposed	1 / 85 (1.18%)	0 / 84 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 85 (1.18%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal behaviour			
subjects affected / exposed	0 / 85 (0.00%)	0 / 84 (0.00%)	0 / 85 (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 / 84 (0.00%)	0 / 85 (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			
Abscess limb			
subjects affected / exposed	0 / 85 (0.00%)	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective myositis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BI 425809 25mg QD	Placebo QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 85 (4.71%)	4 / 170 (2.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 85 (0.00%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 85 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 85 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 85 (1.18%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug dependence			
subjects affected / exposed	1 / 85 (1.18%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fear of disease			
subjects affected / exposed	0 / 85 (0.00%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 85 (0.00%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic symptom			
subjects affected / exposed	0 / 85 (0.00%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Schizophrenia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	1 / 85 (1.18%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 85 (1.18%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 85 (0.00%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective myositis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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 425809 2mg QD	BI 425809 5mg QD	BI 425809 10mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 85 (25.88%)	23 / 84 (27.38%)	14 / 85 (16.47%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 85 (5.88%)	4 / 84 (4.76%)	2 / 85 (2.35%)
occurrences (all)	5	4	2
Headache			
subjects affected / exposed	8 / 85 (9.41%)	10 / 84 (11.90%)	7 / 85 (8.24%)
occurrences (all)	10	11	10
Somnolence			

subjects affected / exposed	2 / 85 (2.35%)	5 / 84 (5.95%)	5 / 85 (5.88%)
occurrences (all)	2	6	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 85 (9.41%)	9 / 84 (10.71%)	7 / 85 (8.24%)
occurrences (all)	8	10	8

Non-serious adverse events	BI 425809 25mg QD	Placebo QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 85 (15.29%)	31 / 170 (18.24%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 85 (3.53%)	6 / 170 (3.53%)	
occurrences (all)	3	6	
Headache			
subjects affected / exposed	8 / 85 (9.41%)	9 / 170 (5.29%)	
occurrences (all)	8	10	
Somnolence			
subjects affected / exposed	2 / 85 (2.35%)	4 / 170 (2.35%)	
occurrences (all)	2	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 85 (4.71%)	13 / 170 (7.65%)	
occurrences (all)	4	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2016	A new exclusion criterion and restrictions on herbal medications were added. In addition, information on a planned substudy with ophthalmologic safety assessments was added.
13 December 2017	To capture additional data on quality of life and social functioning further endpoints were added. Wording in exclusion criteria was updated and clarified.
28 March 2019	The investigator-rated Columbia Suicide Severity Rating Scale (C-SSRS) assessment was added to allow psychiatrists to repeat or validate the telephone assessment in case doubtful reports from the telephone assessment were obtained.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 September 2016	After identifying a new major metabolite (BI 761036), the sponsor communicated a voluntary hold of Phase II to relevant competent authorities on 16-Sep-2016. This was formalized to a full clinical hold of the development program by the Food and Drug Administration (FDA) on 26-Oct-2016. Before start of the hold, 1 patient was screened, but not randomized. Clinical hold was removed by FDA on 21-Nov-2017, the trial was re-initiated with version 3 of the clinical trial protocol, dated 13-Dec-2017.	13 December 2017

Notes:

Limitations and caveats

None reported