



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 | v2 (current) |
| This version publication date | 15 September 2022 |
| First version publication date | 12 February 2021 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setCorrection of previously submitted information. |

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 |
| MATRICES 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 |
| MATRICES 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 (\pm 0.5992) | -3.652 (\pm 0.5890) | -3.078 (\pm 0.5803) | -3.887 (\pm 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 (\pm 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 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 ^[26] |
| Method | MCP-Mod beta model fit |

Notes:

[26] - 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 ^[27] |
| Method | MCP-Mod logistic 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 occurrences (all) | 2 / 85 (2.35%) 2 | 5 / 84 (5.95%) 6 | 5 / 85 (5.88%) 5 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 85 (9.41%) 8 | 9 / 84 (10.71%) 10 | 7 / 85 (8.24%) 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 occurrences (all) | 3 / 85 (3.53%) 3 | 6 / 170 (3.53%) 6 | |
| Headache subjects affected / exposed occurrences (all) | 8 / 85 (9.41%) 8 | 9 / 170 (5.29%) 10 | |
| Somnolence subjects affected / exposed occurrences (all) | 2 / 85 (2.35%) 2 | 4 / 170 (2.35%) 4 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 85 (4.71%) 4 | 13 / 170 (7.65%) 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