# Clinical trial results:
# A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease.

## Summary

| | |
|---|---|
| EudraCT number | 2013-005040-28 |
| Trial protocol | IT PT AT GB BE NL PL |
| Global end of trial date | 10 October 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 24 October 2018 |
| First version publication date | 24 October 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1289.7 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02337907 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 16 November 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 September 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 October 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this trial was to assess efficacy and safety of BI 409306 at doses of 10 milligram (mg), 25 mg and 50 mg once daily, and 25 mg twice daily compared with placebo over a 12-week treatment period in patients with the following criteria: mild dementia of Alzheimer's type, aged ≥55 years, a Mini-Mental-State-Examination (MMSE) between 18 and 26.

Protection of trial subjects:

All patients were informed that they were free to withdraw their consent at any time during the trial without penalty or prejudice. The patients were informed that their personal trialrelated data would be considered confidential and used by BI in accordance with the local data protection laws. The terms and conditions of the insurance cover were available to the investigator and the patients in the Investigator Site File (ISF).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 02 March 2015 |
| 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: 18 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | France: 32 |
| Country: Number of subjects enrolled | Germany: 57 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Netherlands: 24 |
| Country: Number of subjects enrolled | Poland: 78 |
| Country: Number of subjects enrolled | Portugal: 49 |
| Country: Number of subjects enrolled | United Kingdom: 34 |
| Country: Number of subjects enrolled | United States: 71 |
| Worldwide total number of subjects | 386 |
| EEA total number of subjects | 299 |

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) | 55 |
| From 65 to 84 years | 305 |
| 85 years and over | 26 |

## Subject disposition

### Recruitment

Recruitment details:

Phase II, multi-center, double-blind, randomized, placebo controlled trial with mild Alzheimer's disease patients. Additional combined primary and/or secondary endpoints are defined and analyzed for trial 1289.5 and 1289.7, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT02240693

### Pre-assignment

Screening details:

2-week single-blind placebo run-in period before randomization was performed. Patients were not to be randomized to trial if any one of the specific entry criteria were violated. 3 patients were added in the Adults (65 - 84 years) age group due to missing age. Randomization ratio was 1:1:1:1:2 to dose groups of BI 409306 and placebo.

### 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, Data analyst, Assessor |

Blinding implementation details:

This was a double-blind trial.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | BI 409306 10 milligram (mg) once daily (QD) |

Arm description:

Patients were administered orally a tablet of 10 mg BI 409306 once daily for 12 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | BI 409306 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg BI 409306 once daily for 12 weeks

| | |
|---|---|
| **Arm title** | BI 409306 25 mg QD |

Arm description:

Patients were administered orally a tablet of 25 mg BI 409306 once daily for 12 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | BI 409306 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg BI 409306 once daily for 12 weeks

| | |
|---|---|
| **Arm title** | BI 409306 50 mg QD |

Arm description:

Patients were administered orally a tablet of 50 mg BI 409306 once daily for 12 weeks.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | BI 409306 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg BI 409306 once daily for 12 weeks

| | |
|---|---|
| **Arm title** | BI 409306 25 mg twice daily (BID) |

Arm description:

Patients were administered orally a tablet of 25 mg BI 409306 twice daily for 12 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | BI 409306 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg BI 409306 twice daily for 12 weeks

| | |
|---|---|
| **Arm title** | Placebo matching BI 409306 |

Arm description:

Patients were administered orally tablet of Placebo matching BI 409306 once daily or twice daily in order match BID treatment arm, for 12 weeks.

| | |
|---|---|
| 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 matching BI 409306 once or twice daily for 12 weeks

| | |
|---|---|
| **Arm title** | Donepezil QD |

Arm description:

Patients were administered orally over capsulated tablet of Donepezil once daily for 12 weeks.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Donepezil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Once daily for 12 weeks

| **Number of subjects in period 1[1]** | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD |
|---|---|---|---|
| Started | 55 | 53 | 55 |
| Completed | 51 | 49 | 54 |
| Not completed | 4 | 4 | 1 |
| Other than listed | 1 | - | - |
| Adverse event, non-fatal | 1 | 1 | 1 |
| Consent withdrawn by subject | 2 | 3 | - |
| Lost to follow-up | - | - | - |

| **Number of subjects in period 1[1]** | BI 409306 25 mg twice daily (BID) | Placebo matching BI 409306 | Donepezil QD |
|---|---|---|---|
| Started | 55 | 106 | 5 |
| Completed | 51 | 96 | 4 |
| Not completed | 4 | 10 | 1 |
| Other than listed | 1 | 1 | - |
| Adverse event, non-fatal | 1 | 4 | - |
| Consent withdrawn by subject | 2 | 5 | - |
| Lost to follow-up | - | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | BI 409306 10 milligram (mg) once daily (QD) |
| Reporting group description: | |
| Patients were administered orally a tablet of 10 mg BI 409306 once daily for 12 weeks. | |
| Reporting group title | BI 409306 25 mg QD |
| Reporting group description: | |
| Patients were administered orally a tablet of 25 mg BI 409306 once daily for 12 weeks. | |
| Reporting group title | BI 409306 50 mg QD |
| Reporting group description: | |
| Patients were administered orally a tablet of 50 mg BI 409306 once daily for 12 weeks. | |
| Reporting group title | BI 409306 25 mg twice daily (BID) |
| Reporting group description: | |
| Patients were administered orally a tablet of 25 mg BI 409306 twice daily for 12 weeks. | |
| Reporting group title | Placebo matching BI 409306 |
| Reporting group description: | |
| Patients were administered orally tablet of Placebo matching BI 409306 once daily or twice daily in order match BID treatment arm, for 12 weeks. | |
| Reporting group title | Donepezil QD |
| Reporting group description: | |
| Patients were administered orally over capsulated tablet of Donepezil once daily for 12 weeks. | |

| Reporting group values | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD |
|---|---|---|---|
| Number of subjects | 55 | 53 | 55 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous | | | |
| Age at the time of signing informed consent form is presented. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: years | | | |
| arithmetic mean | 73.7 | 74.2 | 73.0 |
| standard deviation | ± 8.4 | ± 7.8 | ± 6.5 |
| Sex: Female, Male | | | |
| Number of subjects is categorized as Male or Female. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| Female | 26 | 30 | 26 |
| Male | 29 | 23 | 29 |
| Race (NIH/OMB) | | | |
| Number of subjects is categorized for race data. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| White | 54 | 53 | 54 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Number of subjects is categorized for ethnicity data. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 2 | 4 |
| Not Hispanic or Latino | 53 | 51 | 51 |
| Unknown or Not Reported | 0 | 0 | 0 |

| **Reporting group values** | BI 409306 25 mg twice daily (BID) | Placebo matching BI 409306 | Donepezil QD |
|---|---|---|---|
| Number of subjects | 55 | 106 | 5 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age Continuous | | | |
| Age at the time of signing informed consent form is presented. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: years | | | |
| arithmetic mean | 74.8 | 74.0 | 79.6 |
| standard deviation | ± 9.1 | ± 7.7 | ± 7.0 |
| Sex: Female, Male | | | |
| Number of subjects is categorized as Male or Female. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| Female | 30 | 48 | 3 |
| Male | 25 | 58 | 2 |
| Race (NIH/OMB) | | | |
| Number of subjects is categorized for race data. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 3 | 0 |
| White | 55 | 103 | 5 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Number of subjects is categorized for ethnicity data. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 2 | 1 |
| Not Hispanic or Latino | 53 | 104 | 4 |
| Unknown or Not Reported | 0 | 0 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 329 | | |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age Continuous | | | |
| Age at the time of signing informed consent form is presented. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Sex: Female, Male | | | |
| Number of subjects is categorized as Male or Female. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| Female | 163 | | |
| Male | 166 | | |
| Race (NIH/OMB) | | | |
| Number of subjects is categorized for race data. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 2 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 3 | | |
| White | 324 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 0 | | |
| Ethnicity (NIH/OMB) | | | |
| Number of subjects is categorized for ethnicity data. Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 13 | | |
| Not Hispanic or Latino | 316 | | |
| Unknown or Not Reported | 0 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | BI 409306 10 milligram (mg) once daily (QD) |
| Reporting group description: | |
| Patients were administered orally a tablet of 10 mg BI 409306 once daily for 12 weeks. | |
| Reporting group title | BI 409306 25 mg QD |
| Reporting group description: | |
| Patients were administered orally a tablet of 25 mg BI 409306 once daily for 12 weeks. | |
| Reporting group title | BI 409306 50 mg QD |
| Reporting group description: | |
| Patients were administered orally a tablet of 50 mg BI 409306 once daily for 12 weeks. | |
| Reporting group title | BI 409306 25 mg twice daily (BID) |
| Reporting group description: | |
| Patients were administered orally a tablet of 25 mg BI 409306 twice daily for 12 weeks. | |
| Reporting group title | Placebo matching BI 409306 |
| Reporting group description: | |
| Patients were administered orally tablet of Placebo matching BI 409306 once daily or twice daily in order match BID treatment arm, for 12 weeks. | |
| Reporting group title | Donepezil QD |
| Reporting group description: | |
| Patients were administered orally over capsulated tablet of Donepezil once daily for 12 weeks. | |
| Subject analysis set title | Pooled BI 409306 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Patients were administered orally a tablet of BI 409306 (10 mg, 25 mg, 50 mg once daily and 25 mg twice daily)for 12 weeks. | |
| Subject analysis set title | Pooled BI 409306 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Patients were administered orally a tablet of BI 409306 (10 mg, 25 mg, 50 mg once daily and 25 mg twice daily)for 12 weeks. | |

### Primary: Change from baseline in Neuropsychological Test Battery in total z-score after 12-week treatment.

| | |
|---|---|
| End point title | Change from baseline in Neuropsychological Test Battery in total z-score after 12-week treatment.[1] |
| End point description: | |
| Neuropsychological Test Battery (NTB) response, defined as change from baseline in total z-score after 12 weeks of treatment. The NTB consists of 9 validated components. Raw scores on each of the 9 NTB tests were converted to z-scores using the baseline means and standard deviations (SDs) for each test. The resultant z-scores were averaged to obtain a total z-score, incorporating all 9 NTB tests. Least Squares Mean is actually an adjusted mean change from baseline. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and 12 weeks | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD | BI 409306 25 mg twice daily (BID) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 47[2] | 44[3] | 51[4] | 45[5] |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | 0.13 (± 0.059) | 0.17 (± 0.061) | 0.16 (± 0.056) | 0.01 (± 0.060) |

Notes:

[2] - FAS (OC)

[3] - FAS (OC)

[4] - FAS (OC)

[5] - FAS (OC)

| End point values | Placebo matching BI 409306 | Pooled BI 409306 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 83[6] | 214[7] | | |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | 0.15 (± 0.045) | 0.12 (± 0.30) | | |

Notes:

[6] - FAS (OC)

[7] - FAS (OC)

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 10 milligram (mg) once daily (QD) v Placebo matching BI 409306 |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[8] |
| P-value | = 0.7907 [9] |
| Method | Mixed Model Repeated Measurement (MMRM) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.163 |
| upper limit | 0.124 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.073 |

Notes:

[8] - H0: The dose group with the peak response in the respective model Mean NTB response = Mean NTB response of placebo. Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

[9] - p-value was nominal and not adjusted.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | = 0.7622 [11] |
| Method | Mixed Model Repeated Measurement (MMRM) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.125 |
| upper limit | 0.171 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.075 |

Notes:

[10] - H0: The dose group with the peak response in the respective model Mean NTB response = Mean NTB response of placebo. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[11] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 50 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 134 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.8789 [13] |
| Method | Mixed Model Repeated Measurement (MMRM) |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.13 |
| upper limit | 0.152 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.071 |

Notes:

[12] - H0: The dose group with the peak response in the respective model Mean NTB response = Mean NTB response of placebo. Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[13] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as

well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg twice daily (BID) v Placebo matching BI 409306 |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[14] |
| P-value | = 0.0609 [15] |
| Method | Mixed Model Repeated Measurement (MMRM) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.285 |
| upper limit | 0.006 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.074 |

Notes:

[14] - H0: The dose group with the peak response in the respective model Mean NTB response = Mean NTB response of placebo. Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[15] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 5 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | Placebo matching BI 409306 v Pooled BI 409306 |
| Number of subjects included in analysis | 297 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[16] |
| P-value | = 0.5687 [17] |
| Method | Mixed Model Repeated Measurement (MMRM) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.135 |
| upper limit | 0.074 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.053 |

Notes:

[16] - H1-0: Mean NTB response of pooled doses of 10 mg QD, 25 mg QD, 25 mg BID and 50 mg QD = Mean NTB response of placebo. Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[17] - p-value was nominal and not adjusted.

## Secondary: Change from baseline in Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) total score after 12-week treatment

| | |
|---|---|
| End point title | Change from baseline in Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) total score after 12-week treatment[18] |

End point description:

Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) is a rating scale used to assess basic and instrumental activities of daily living. In the full version of the scale, 23 items are rated by the investigator using information supplied by the caregiver. Each item has a score range varying from 0-3 to 0-5. The sum score can range from 0 to 78. Higher scores indicate better function. Least Squares Mean is actually an adjusted mean change from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and 12 weeks

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD | BI 409306 25 mg twice daily (BID) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54[19] | 50[20] | 55[21] | 55[22] |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | 0.10 (± 0.853) | -0.99 (± 0.892) | 0.35 (± 0.847) | -1.07 (± 0.855) |

Notes:

[19] - FAS

[20] - FAS

[21] - FAS

[22] - FAS

| **End point values** | Placebo matching BI 409306 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 101[23] | | | |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | -0.58 (± 0.639) | | | |

Notes:

[23] - FAS

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 11 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| Comparison groups | BI 409306 10 milligram (mg) once daily (QD) v Placebo matching BI 409306 |
|---|---|
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[24] |
| P-value | = 0.5287 [25] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |

| | |
|---|---|
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.43 |
| upper limit | 2.77 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.066 |

Notes:

[24] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[25] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 12 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[26] |
| P-value | = 0.7105 [27] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.57 |
| upper limit | 1.76 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.099 |

Notes:

[26] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[27] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 13 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| | |
|---|---|
| Comparison groups | BI 409306 50 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[28] |
| P-value | = 0.3822 [29] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

| | |
|---|---|
| lower limit | -1.16 |
| upper limit | 3.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.064 |

Notes:

[28] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[29] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 14 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg twice daily (BID) v Placebo matching BI 409306 |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[30] |
| P-value | = 0.6472 [31] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.59 |
| upper limit | 1.61 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.066 |

Notes:

[30] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[31] - p-value was nominal and not adjusted.

## Secondary: Change from baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) total score after 12-week treatment

| End point title | Change from baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) total score after 12-week treatment[32] |
|---|---|

End point description:

Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) is obtained through semi-structured interviews of patients and informants, and cognitive functioning is rated in 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). Least Squares Mean is actually an adjusted mean change from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and 12 weeks

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD | BI 409306 25 mg twice daily (BID) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54[33] | 50[34] | 55[35] | 55[36] |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | 0.1 (± 0.23) | 0.3 (± 0.23) | 0.1 (± 0.21) | 0.2 (± 0.22) |

Notes:

[33] - FAS

[34] - FAS

[35] - FAS

[36] - FAS

| End point values | Placebo matching BI 409306 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 101[37] | | | |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | 0.1 (± 0.16) | | | |

Notes:

[37] - FAS

## Statistical analyses

| Statistical analysis title | Statistical Analysis 15 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 10 milligram (mg) once daily (QD) v Placebo matching BI 409306 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[38] |
| P-value | = 0.7551 [39] |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.28 |

Notes:

[38] - Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[39] - p-value was nominal and not adjusted.

| Statistical analysis title | Statistical Analysis 16 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[40] |
| P-value | = 0.3643 [41] |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | 0.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.28 |

Notes:

[40] - Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[41] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 17 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 50 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[42] |
| P-value | = 0.7822 [43] |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | 0.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.27 |

Notes:

[42] - Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[43] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 18 |
|---|---|

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, current Acetylcholine Esterase Inhibitor (AChEI) use (Yes, No), and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg twice daily (BID) v Placebo matching BI 409306 |

| | |
|---|---|
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[44] |
| P-value | = 0.6889 [45] |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | 0.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.28 |

Notes:

[44] - Kenward−Roger was used to model degrees of freedom. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[45] - p-value was nominal and not adjusted.

## Secondary: Change from baseline in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog11) total score after 12-week treatment

| | |
|---|---|
| End point title | Change from baseline in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog11) total score after 12-week treatment[46] |

End point description:

Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog11) is an 11-item cognitive subscale that objectively measures memory, language, orientation, and praxis with a total score range of 0 to 70. Least Squares Mean is actually an adjusted mean change from baseline.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline and 12 weeks

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| **End point values** | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD | BI 409306 25 mg twice daily (BID) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 54[47] | 50[48] | 55[49] | 55[50] |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | 1.14 (± 0.738) | 0.94 (± 0.776) | 1.11 (± 0.746) | 2.29 (± 0.746) |

Notes:

[47] - FAS

[48] - FAS

[49] - FAS

[50] - FAS

| **End point values** | Placebo matching BI 409306 | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |

| | | | | |
|---|---|---|---|---|
| Number of subjects analysed | 101[51] | | | |
| Units: Unit on scale | | | | |
| least squares mean (standard error) | -0.18 (± 0.568) | | | |

Notes:

[51] - FAS

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 19 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| | |
|---|---|
| Comparison groups | BI 409306 10 milligram (mg) once daily (QD) v Placebo matching BI 409306 |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[52] |
| P-value | = 0.1595 [53] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.52 |
| upper limit | 3.15 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.933 |

Notes:

[52] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.

[53] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 20 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[54] |
| P-value | = 0.2455 [55] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.77 |
| upper limit | 3.01 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Dispersion value | 0.962 |

Notes:

[54] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[55] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 21 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| | |
|---|---|
| Comparison groups | BI 409306 50 mg QD v Placebo matching BI 409306 |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[56] |
| P-value | = 0.1732 [57] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.57 |
| upper limit | 3.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.94 |

Notes:

[56] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[57] - p-value was nominal and not adjusted.

| **Statistical analysis title** | Statistical Analysis 22 |
|---|---|

Statistical analysis description:

The dependent variable was the change from the baseline score at Week 12. The model included fixed, categorical covariates of treatment as well as fixed continuous covariates of baseline score.

| | |
|---|---|
| Comparison groups | BI 409306 25 mg twice daily (BID) v Placebo matching BI 409306 |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[58] |
| P-value | = 0.0088 [59] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 4.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.936 |

Notes:

[58] - Analyses of covariance (ANCOVA) were used to assess between−group differences in the modelled changes from baseline to Week 12. The mean difference is actually adjusted mean of

difference and the dispersion value is standard error of differences.
[59] - p-value was nominal and not adjusted.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication until 7 days after last administration of BI 409306, up to 16 weeks.

Adverse event reporting additional description:

The treated set (TS) used (all patients who were randomised and treated with at least one dose of trial medication.) for safety assessment.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | BI 409306 10 milligram (mg) once daily (QD) |

Reporting group description:

Patients were administered orally a tablet of 10 mg BI 409306 once daily for 12 weeks.

| | |
|---|---|
| Reporting group title | BI 409306 25 mg QD |

Reporting group description:

Patients were administered orally a tablet of 25 mg BI 409306 once daily for 12 weeks.

| | |
|---|---|
| Reporting group title | BI 409306 50 mg QD |

Reporting group description:

Patients were administered orally a tablet of 50 mg BI 409306 once daily for 12 weeks.

| | |
|---|---|
| Reporting group title | BI 409306 25 mg twice daily (BID) |

Reporting group description:

Patients were administered orally a tablet of 25 mg BI 409306 twice daily for 12 weeks.

| | |
|---|---|
| Reporting group title | Placebo matching BI 409306 |

Reporting group description:

Patients were administered orally tablet of Placebo matching BI 409306 once daily or twice daily in order match BID treatment arm, for 12 weeks.

| | |
|---|---|
| Reporting group title | Donepezil QD |

Reporting group description:

Patients were administered orally over capsulated tablet of Donepezil once daily for 12 weeks.

| Serious adverse events | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 53 (5.66%) | 1 / 55 (1.82%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |

| | | | |
|---|---|---|---|
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Injury, poisoning and procedural complications | | | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Investigations | | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 53 (1.89%) | 0 / 55 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 53 (1.89%) | 0 / 55 (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 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 53 (0.00%) | 0 / 55 (0.00%) |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 53 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 53 (1.89%) | 0 / 55 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Gastrointestinal disorders | | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (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 | | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | BI 409306 25 mg twice daily (BID) | Placebo matching BI 409306 | Donepezil QD |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 8 / 106 (7.55%) | 0 / 5 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Injury, poisoning and procedural complications | | | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Investigations | | | |
| Electrocardiogram QT prolonged | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 0 / 5 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 0 / 5 (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 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 0 / 5 (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 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 0 / 5 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |

| | | | |
|---|---|---|---|
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 106 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 0 / 5 (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 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Gastrointestinal disorders | | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 106 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (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 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | BI 409306 10 milligram (mg) once daily (QD) | BI 409306 25 mg QD | BI 409306 50 mg QD |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 9 / 53 (16.98%) | 7 / 55 (12.73%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 3 / 55 (5.45%) |
| occurrences (all) | 0 | 0 | 3 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 5 / 53 (9.43%) | 1 / 55 (1.82%) |
| occurrences (all) | 2 | 5 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 0 / 53 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 4 / 53 (7.55%) | 3 / 55 (5.45%) |
| occurrences (all) | 1 | 4 | 3 |

| Non-serious adverse events | BI 409306 25 mg twice daily (BID) | Placebo matching BI 409306 | Donepezil QD |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 8 / 106 (7.55%) | 1 / 5 (20.00%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 106 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 5 / 106 (4.72%) | 0 / 5 (0.00%) |

| | | | |
|---|---|---|---|
| occurrences (all) | 1 | 5 | 0 |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 2 / 106 (1.89%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 106 (0.94%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 27 July 2015 | The donepezil arm was dropped from the trial and therefore reference to donepezil was removed. Sample size and treatment groups, inclusion criteria, trial objectives and description of Interactive Response Technology (IRT) and trial medications were adapted accordingly. The reason for this change was that Acetylcholine Esterase Inhibitors (AChEIs) (including donepezil) are the standard treatment in Alzheimer's Disease. Therefore, the trial design was changed to allow both treatment-naïve patients and patients on standard of care to enter the trial. This change enabled the analysis of the treatment effect in the expected target population for the trial medication. As a result, stable concomitant use of AChEIs was permitted and current AChEI use (Yes, No) was added as a stratification factor to the primary analysis model and randomization.<br><br>The number of neuropsychological scales was reduced to reduce patient burden during the visits. This did not have an impact on the clinical validity of primary and secondary analyses, as many items of the removed scales were still part of the remaining assessments. The amendment allowed use of strong or moderate Cytochrome P450 (CYP)3A4 inhibitors as a clinical trial did not show an impact on exposure to BI 409306 after CYP3A4 inhibition.<br><br>To allow patients with a contraindication for Magnetic Resonance Imaging (MRI) to enter the trial, the use of a Cranial Computer Tomography (CCT) to exclude other disorders causing dementia was allowed. The analysis models for secondary endpoints with different number of data collection visits were clarified. Text clarifications were also implemented. |
| 01 September 2016 | Iintroduced to power the trial for a smaller effect size. The sample size was changed to a total of N=354, which allowed detecting an effect size of 0.45 with 80% power, 2-sided alpha of 0.05. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

There were 5 patients who were randomised to donepezil arm which was dropped from the trial with protocol amendment. No further patients were randomised to this arm, but patients already randomised continued in the trial as originally planned.

Notes: