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

Summary

EudraCT number	2013-005031-24
Trial protocol	DE IT PT ES BE AT NL GB
Global end of trial date	09 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	1289.5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02240693
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	20 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2017
Global end of trial reached?	Yes
Global end of trial date	09 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy, safety, and tolerability of different doses of BI 409306 compared with placebo in treatment of prodromal Alzheimer's disease (AD)

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 160
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Spain: 85
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 63
Worldwide total number of subjects	504
EEA total number of subjects	414

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)	78
From 65 to 84 years	402
85 years and over	24

Subject disposition

Recruitment

Recruitment details:

A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease

Pre-assignment

Screening details:

For this trial, patients were randomised at 36 sites in 11 countries. Following an initial Screening Visit and a single blinded 2-week placebo run-in period, patients who qualified according to the in- and exclusion criteria were randomised to one of the five treatment groups

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

Blinding implementation details:

This trial incorporated a double-blind, double-dummy trial design

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 Placebo matching 10 mg/25 mg/ 50 mg BI 409306 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 10 mg/25 mg/ 50 mg BI 409306 QD/BID 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	22	21	21
Completed	22	21	17
Not completed	0	0	4
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	-	-	-
Other than specified	-	-	2

Number of subjects in period 1[1]	BI 409306 25 mg twice daily (BID)	Placebo matching BI 409306
Started	21	43
Completed	20	42
Not completed	1	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	1

Other than specified	-	-

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 Placebo matching 10 mg/25 mg/ 50 mg BI 409306 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	22	21	21
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	72.3	74.1	73.3
standard deviation	± 5.4	± 8.1	± 5.1
Sex: Female, Male			
Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication.			
Units: Subjects			
Female	10	12	8
Male	12	9	13
Race (NIH/OMB)			
Race data is presented below; Ethnicity was not reported in this trial			
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	0	0
White	22	21	21
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Neuropsychological Test Battery (NTB) Total			
Baseline cognitive assessment data- NTB total z-score. 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.			
Units: Unit on scale			
arithmetic mean	0.07	0.02	-0.02
standard deviation	± 0.70	± 0.75	± 0.72

Reporting group values	BI 409306 25 mg twice daily (BID)	Placebo matching BI 409306	Total
Number of subjects	21	43	128
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	71.9	72.2	
standard deviation	± 6.0	± 6.5	-
Sex: Female, Male			
Treated Set (TS) included all patients who were randomised and treated with at least one dose of trial medication.			
Units: Subjects			
Female	13	28	71
Male	8	15	57
Race (NIH/OMB)			
Race data is presented below; Ethnicity was not reported in this trial			
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	0	0
White	21	43	128
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Neuropsychological Test Battery (NTB) Total			
Baseline cognitive assessment data- NTB total z-score. 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.			
Units: Unit on scale			
arithmetic mean	-0.02	-0.03	
standard deviation	± 0.61	± 0.63	-

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 Placebo matching 10 mg/25 mg/ 50 mg BI 409306 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.
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. The full analysis set (FAS): FAS includes all randomised patients who were treated with at least one dose of trial medication and had a baseline and at least one post-baseline on-treatment primary endpoint NTB or secondary endpoint assessment. Observed cases (OC).	
End point type	Primary
End point timeframe:	
Baseline and 12 weeks	

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	20[1]	19[2]	16[3]	18[4]
Units: Unit on scale				
least squares mean (standard error)	0.35 (± 0.061)	0.20 (± 0.063)	0.26 (± 0.065)	0.32 (± 0.064)

Notes:

[1] - FAS (OC)

[2] - FAS (OC)

[3] - FAS (OC)

[4] - FAS (OC)

End point values	Placebo matching BI 409306	Pooled BI 409306		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	39[5]	73[6]		
Units: Unit on scale				
least squares mean (standard error)	0.27 (± 0.043)	0.29 (± 0.031)		

Notes:

[5] - FAS (OC)

[6] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 10 milligram (mg) once daily (QD) v Placebo matching BI 409306
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.3236 [8]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.223
Variability estimate	Standard error of the mean
Dispersion value	0.075

Notes:

[7] - 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.

[8] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 25 mg QD v Placebo matching BI 409306
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.3694 [10]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.076

Notes:

[9] - 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.
[10] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 50 mg QD v Placebo matching BI 409306
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.8374 [12]
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	-0.171
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.078

Notes:

[11] - 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.

[12] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 25 mg twice daily (BID) v Placebo matching BI 409306
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.5484 [14]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.106
upper limit	0.199
Variability estimate	Standard error of the mean
Dispersion value	0.077

Notes:

[13] - 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
[14] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	Placebo matching BI 409306 v Pooled BI 409306
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.7905 [16]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.121
Variability estimate	Standard error of the mean
Dispersion value	0.054

Notes:

[15] - 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

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

Secondary: Change from baseline in ADCS-MCI-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living for patients with mild cognitive impairment) total score after 12-week treatment

End point title	Change from baseline in ADCS-MCI-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living for patients with mild cognitive impairment) total score after 12-week treatment

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

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	19[17]	18[18]	20[19]	17[20]
Units: Unit on scale				
least squares mean (standard error)	0.24 (± 0.896)	1.79 (± 0.921)	-0.10 (± 0.875)	0.80 (± 0.947)

Notes:

[17] - FAS

[18] - FAS

[19] - FAS

[20] - FAS

End point values	Placebo matching BI 409306			
Subject group type	Reporting group			
Number of subjects analysed	37[21]			
Units: Unit on scale				
least squares mean (standard error)	0.38 (± 0.642)			

Notes:

[21] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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	56
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.8973 [23]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.33
upper limit	2.04
Variability estimate	Standard error of the mean
Dispersion value	1.102

Notes:

[22] - 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
[23] - p-value was nominal and not adjusted.

Statistical analysis title	Statistical Analysis 2

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	55
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.2141 [25]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	3.63
Variability estimate	Standard error of the mean
Dispersion value	1.122

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 3

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	57
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.6553 [27]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.64
upper limit	1.67
Variability estimate	Standard error of the mean
Dispersion value	1.085

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 4

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	54
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.7166 [29]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	2.69
Variability estimate	Standard error of the mean
Dispersion value	1.144

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.

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

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

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	21[30]	19[31]	16[32]	18[33]
Units: Unit on scale				
least squares mean (standard error)	0.0 (± 0.19)	0.4 (± 0.20)	-0.1 (± 0.22)	0.1 (± 0.21)

Notes:

[30] - FAS

[31] - FAS

[32] - FAS

[33] - FAS

End point values	Placebo matching BI 409306			
Subject group type	Reporting group			
Number of subjects analysed	40[34]			
Units: Unit on scale				
least squares mean (standard error)	0.1 (± 0.14)			

Notes:

[34] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model Repeated Measurement (MMRM) includes fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 10 milligram (mg) once daily (QD) v Placebo matching BI 409306
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.9491 [36]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.46
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[35] - The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[36] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 25 mg QD v Placebo matching BI 409306
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.1699 [38]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.84
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[37] - The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[38] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 50 mg QD v Placebo matching BI 409306
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.4948 [40]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[39] - The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[40] - 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, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline, and baseline-by-visit interaction.
Kenward−Roger was used to model degrees of freedom.

Comparison groups	BI 409306 25 mg twice daily (BID) v Placebo matching BI 409306
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.7548 [42]
Method	Mixed Model Repeated Measurement (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[41] - The mean difference is actually adjusted mean of difference and the dispersion value is standard error of differences.
[42] - 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

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

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	19[43]	17[44]	19[45]	19[46]
Units: Unit on scale				
least squares mean (standard error)	0.98 (± 0.885)	0.62 (± 0.935)	0.12 (± 0.875)	-1.27 (± 0.875)

Notes:

[43] - FAS

[44] - FAS

[45] - FAS

[46] - FAS

End point values	Placebo matching BI 409306			
Subject group type	Reporting group			
Number of subjects analysed	38[47]			
Units: Unit on scale				
least squares mean (standard error)	1.24 (± 0.619)			

Notes:

[47] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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	57
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.8137 [49]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	1.89
Variability estimate	Standard error of the mean
Dispersion value	1.081

Notes:

[48] - 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.

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

Statistical analysis title	Statistical Analysis 2

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	55
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.5801 [51]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	1.12

Notes:

[50] - 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.
[51] - p-value was nominal and not adjusted.

Statistical analysis title	Statistical Analysis 3

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	57
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.2978 [53]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.25
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	1.072

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 4

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	57
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.0209 [55]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.64
upper limit	-0.39
Variability estimate	Standard error of the mean
Dispersion value	1.072

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.

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 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	0 / 22 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	0 / 21 (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			
Haematuria			

subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	0 / 21 (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	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	1 / 43 (2.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BI 409306 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	12 / 22 (54.55%)	13 / 21 (61.90%)	14 / 21 (66.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 22 (9.09%)	0 / 21 (0.00%)	4 / 21 (19.05%)
occurrences (all)	3	0	4
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 21 (14.29%)	1 / 21 (4.76%)
occurrences (all)	3	4	2
Nervous system disorders			
Headache			

subjects affected / exposed	2 / 22 (9.09%)	4 / 21 (19.05%)	3 / 21 (14.29%)
occurrences (all)	2	4	3
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Muscle spasms			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	0 / 21 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	BI 409306 25 mg twice daily (BID)	Placebo matching BI 409306	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 21 (61.90%)	22 / 43 (51.16%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 21 (0.00%)	4 / 43 (9.30%)	
occurrences (all)	0	5	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 21 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	2 / 21 (9.52%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2014	Amendment 1 introduced changes to inclusion criteria #7 and #8, to be in accordance with ICH-GCP. The option of consent by a legal representative was deleted throughout the CTP.Based on scientific advice from external experts, the cut-offs for the MMSE were changed and a cut-off for the global CDR-score was introduced to more appropriately describe the target population. The amendment introduced changes to exclusion criterion #13: The acceptable methods of birth control for female patients of child-bearing potential were changed based on authority feedback. An additional exclusion criterion concerning birth control for male patients was added. Relevant CYP2C19 inducers were added to the list of restricted concomitant medication. Amendment 1 added the option of doing the neuropsychological assessments of Visit 3 on the day before, i.e. on the last day of the screening period, to increase feasibility. The change was made based on feedback from investigators. Based on feedback from authorities, Visit 4 was changed to be a clinic visit. Serology was added, to be done in case of reported liver injury. Several changes were introduced to align the CTP with project standards: - The follow-up period was extended to 4 weeks - Exclusion criterion #10 was updated to include DSM-V - The wording on reporting of visual AEs was moved and changed - The instructions for assessment of safety laboratory parameters were reworded; - Vitamin B12 and Folate were added. - Transmitting ECGs to the vendor was introduced, instead of electronic storage at the site only. - The instructions for neuropsychological assessments were reworded.
03 August 2015	Amendment 3 specified the definition of eligible patients further. According to feedback from the investigators, patients with prodromal AD usually ask for treatment and sometimes take available AD medication, despite the fact that there are no treatments registered for prodromal AD. In order to avoid unnecessary limitation to the recruitment, patients who previously took AD treatment were allowed to enter the trial. The restrictions for intake of drugs for treatment of AD during trial participation were updated accordingly, to clarify that patients who took AD treatment previously were not allowed to use these treatments during the trial. The number of neuropsychological scales was reduced to reduce patient burden during the visits. This did not have an impact on 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 CYP3A4 inhibitors as a clinical trial did not show an impact on exposure to BI 409306 after CYP3A4 inhibition. To allow patients with a contraindication for MRI to enter the trial, the use of a CCT to exclude other disorders causing prodromal AD was allowed. The analysis models for secondary endpoints with different number of data collection visits were clarified. Text clarifications were also implemented.

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.

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

Notes: