EU Clinical Trials Register

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
Consent withdrawn by subject	2	3	-
Adverse event, non-fatal	1	1	1
Lost to follow-up	-	-	-
Other than listed	1	-	-

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
Consent withdrawn by subject	2	5	-
Adverse event, non-fatal	1	4	-
Lost to follow-up	-	-	1
Other than listed	1	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			
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			
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			
standard deviation	-		
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
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

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
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
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
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
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
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
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			

	BI 409306 25 mg twice daily (BID)	Placebo matching BI 409306	Donepezil QD
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
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
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
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

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

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
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
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
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
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%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 55 (3.64%)	5 / 53 (9.43%)	1 / 55 (1.82%)
occurrences (all)	2	5	1
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
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%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 55 (1.82%)	5 / 106 (4.72%)	0 / 5 (0.00%)
occurrences (all)	1	5	0
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
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. 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. 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: