Clinical trial results:
A multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy and safety of orally administered BI 425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease.

Summary

EudraCT number	2015-005438-24
Trial protocol	AT HU NO FI GR GB ES FR IT
Global end of trial date	11 October 2019

Results information

Result version number	v2 (current)
This version publication date	24 December 2020
First version publication date	24 October 2020
Version creation reason	• New data added to full data set Addition of NCT Number in section Trial Information / Additional Trial Identifier.

Trial information

Trial identification

Sponsor protocol code	1346.23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02788513
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2019
Global end of trial reached?	Yes
Global end of trial date	11 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to assess safety, tolerability, and efficacy of different doses of BI 425809 compared with Placebo in patients with cognitive impairment due to Alzheimer's Disease.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.
For two subjects in the Adults (18-64 years) it does not reflect their true age. Their actual age is unknown. Subjects counted for Afghanistan does not reflect their true country. Their actual country is unknown.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Canada: 69
Country: Number of subjects enrolled	Finland: 32
Country: Number of subjects enrolled	France: 114
Country: Number of subjects enrolled	Germany: 79
Country: Number of subjects enrolled	Greece: 52
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Japan: 70
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	United States: 221
Country: Number of subjects enrolled	Afghanistan: 2
Worldwide total number of subjects	851
EEA total number of subjects	489

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)	147
From 65 to 84 years	666
85 years and over	38

Subject disposition

Recruitment

Recruitment details:

This is a multi-centre, double-blind, parallel-group, randomised controlled study to investigate efficacy and safety of orally administered BI 425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease.

Pre-assignment

Screening details:

Subjects were screened for eligibility prior to participation. Subjects attended a specialist site which ensured that they strictly met all eligibility criteria. Subjects were not to be allocated to a treatment group if any of the criteria were violated.
One subject was randomized by error via Interactive Response Technology but never took a drug.

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:

Double-blind trial

Arms

Are arms mutually exclusive?	Yes
Arm title	2 mg BI 425809

Arm description:

Participants in dose group 1 were orally administered 2 tablets of 1 milligrams (mg) of BI 425809 (Total: 2 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

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

Dosage and administration details:

Participants in dose group 1 were orally administered 2 tablets of 1 milligrams (mg) of BI 425809 (Total: 2 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Arm title	5 mg BI 425809

Arm description:

Participants in dose group 2 were orally administered 1 tablet of 5 mg of BI 425809 together with 1 tablet of 1 mg / 5 mg and 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

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

Dosage and administration details:

Participants in dose group 2 were orally administered 1 tablet of 5 mg of BI 425809 together with 1 tablet of 1 mg / 5 mg and 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Arm title	10 mg BI 425809

Arm description:

Participants in dose group 3 were orally administered 2 tablets of 5 mg of BI 425809 (Total: 10 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

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

Dosage and administration details:

Participants in dose group 3 were orally administered 2 tablets of 5 mg of BI 425809 (Total: 10 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Arm title	25 mg BI 425809

Arm description:

Participants in dose group 4 were orally administered 1 tablet of 25 mg of BI 425809 together with 2 tablets of 1 mg / 5 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

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

Dosage and administration details:

Participants in dose group 4 were orally administered 1 tablet of 25 mg of BI 425809 together with 2 tablets of 1 mg / 5 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Arm title	Placebo group

Arm description:

Participants in the placebo group were orally administered 2 tablets of 1 mg / 5 mg and 1 tablet of 25 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

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:

Participants in the placebo group were orally administered 2 tablets of 1 mg / 5 mg and 1 tablet of 25 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Number of subjects in period 1[1]	2 mg BI 425809	5 mg BI 425809	10 mg BI 425809
Started	123	122	122
Completed	114	114	114
Not completed	9	8	8
Decision by the study team	-	-	-
Protocol deviation	-	-	1
Adverse event, non-fatal	5	8	4
Subject decided to stop taking treatment	-	-	1
Consent withdrawn by subject	3	-	2
Lost to follow-up	1	-	-

Number of subjects in period 1[1]	25 mg BI 425809	Placebo group
Started	123	120
Completed	117	115
Not completed	6	5
Decision by the study team	-	1
Protocol deviation	1	-
Adverse event, non-fatal	2	2
Subject decided to stop taking treatment	-	-
Consent withdrawn by subject	3	1
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject was screened/randomized by error via Interactive Response Technology (IRT) but never took a drug.

Baseline characteristics

Reporting groups	
Reporting group title	2 mg BI 425809
Reporting group description:	
Participants in dose group 1 were orally administered 2 tablets of 1 milligrams (mg) of BI 425809 (Total: 2 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.	
Reporting group title	5 mg BI 425809
Reporting group description:	
Participants in dose group 2 were orally administered 1 tablet of 5 mg of BI 425809 together with 1 tablet of 1 mg / 5 mg and 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.	
Reporting group title	10 mg BI 425809
Reporting group description:	
Participants in dose group 3 were orally administered 2 tablets of 5 mg of BI 425809 (Total: 10 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.	
Reporting group title	25 mg BI 425809
Reporting group description:	
Participants in dose group 4 were orally administered 1 tablet of 25 mg of BI 425809 together with 2 tablets of 1 mg / 5 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.	
Reporting group title	Placebo group
Reporting group description:	
Participants in the placebo group were orally administered 2 tablets of 1 mg / 5 mg and 1 tablet of 25 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.	

Reporting group values	2 mg BI 425809	5 mg BI 425809	10 mg BI 425809
Number of subjects	123	122	122
Age categorical			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	23	8
From 65-84 years	97	90	107
85 years and over	4	9	7
Age Continuous			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: years			

arithmetic mean	72.3	72.5	74.4
standard deviation	± 7.5	± 8.2	± 6.9

Sex: Female, Male			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Participants			
Female	68	62	66
Male	55	60	56
Ethnicity (NIH/OMB)			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Subjects			
Hispanic or Latino	17	22	11
Not Hispanic or Latino	101	98	106
Unknown or Not Reported	5	2	5
Race (NIH/OMB)			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	11	10	12
Native Hawaiian or Other Pacific Islander	0	2	1
Black or African American	10	5	4
White	97	103	100
More than one race	0	0	0
Unknown or Not Reported	5	2	5
ADASCOG baseline cognitive assessment data			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: score on a scale			
arithmetic mean	18.8	18.8	19.6
standard deviation	± 7.9	± 7.4	± 7.8

Reporting group values	25 mg BI 425809	Placebo group	Total
Number of subjects	123	120	610
Age categorical			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

Adults (18-64 years)	18	23	94
From 65-84 years	101	92	487
85 years and over	4	5	29
Age Continuous			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: years			
arithmetic mean	72.9	72.4	
standard deviation	± 7.7	± 7.9	-
Sex: Female, Male			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Participants			
Female	64	64	324
Male	59	56	286
Ethnicity (NIH/OMB)			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Subjects			
Hispanic or Latino	16	20	86
Not Hispanic or Latino	103	94	502
Unknown or Not Reported	4	6	22
Race (NIH/OMB)			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	14	11	58
Native Hawaiian or Other Pacific Islander	1	2	6
Black or African American	3	8	30
White	102	93	495
More than one race	0	0	0
Unknown or Not Reported	3	6	21
ADASCOG baseline cognitive assessment data			
Treated set (TS): The TS included all randomized subjects who had been enrolled and treated with at least 1 dose of study drug. The treated set was used for demographics, baseline characteristics and safety analyses.			
Units: score on a scale			
arithmetic mean	19.6	18.2	
standard deviation	± 7.3	± 8.0	-

End points

End points reporting groups

Reporting group title	2 mg BI 425809

Reporting group description:

Participants in dose group 1 were orally administered 2 tablets of 1 milligrams (mg) of BI 425809 (Total: 2 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	5 mg BI 425809

Reporting group description:

Participants in dose group 2 were orally administered 1 tablet of 5 mg of BI 425809 together with 1 tablet of 1 mg / 5 mg and 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	10 mg BI 425809

Reporting group description:

Participants in dose group 3 were orally administered 2 tablets of 5 mg of BI 425809 (Total: 10 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	25 mg BI 425809

Reporting group description:

Participants in dose group 4 were orally administered 1 tablet of 25 mg of BI 425809 together with 2 tablets of 1 mg / 5 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	Placebo group

Reporting group description:

Participants in the placebo group were orally administered 2 tablets of 1 mg / 5 mg and 1 tablet of 25 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Subject analysis set title	2 mg BI 425809
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in dose group 1 were orally administered 2 tablets of 1 milligrams (mg) of BI 425809 (Total: 2 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Subject analysis set title	5 mg BI 425809
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in dose group 2 were orally administered 1 tablet of 5 mg of BI 425809 together with 1 tablet of 1 mg / 5 mg and 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Subject analysis set title	10 mg BI 425809
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in dose group 3 were orally administered 2 tablets of 5 mg of BI 425809 (Total: 10 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Subject analysis set title	25 mg BI 425809
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in dose group 4 were orally administered 1 tablet of 25 mg of BI 425809 together with 2 tablets of 1 mg / 5 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Subject analysis set title	Placebo group

Subject analysis set type	Full analysis

Subject analysis set description:

Participants in the placebo group were orally administered 2 tablets of 1 mg / 5 mg and 1 tablet of 25 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Primary: Change from baseline in ADAS-Cog11 (Alzheimer's Disease Assessment Scale-Cognitive subscale 11 item) total score after 12 weeks of treatment

End point title	Change from baseline in ADAS-Cog11 (Alzheimer's Disease Assessment Scale-Cognitive subscale 11 item) total score after 12 weeks of treatment

End point description:

ADAS-Cog11 is a 11-item cognitive subscale that objectively measures memory, language, orientation and praxis with a total score range of 0 to 70, with lower scores indicating less severe impairment. Negative change is an improvement from BL.

MCPmod + MMRM combination is used for primary analysis. MMRM included fixed, categorical covariates of treatment, visit, BL Mini Mental State Examination (>=20, <20) and treatment-by-visit interaction, as well as the continuous fixed covariates of BL and BL-by-visit interaction. Patient was considered as random effect. The unstructured covariance structure was used to model the within patient measurements. The same MMRM model used in the primary analysis is used for the secondary analysis.

Full analysis set (FAS): all randomised patients who were treated with at least one dose of trial medication, had a BL and at least one corresponding post-BL on-treatment efficacy assessment for any efficacy EP. FAS is used for efficacy analysis.

End point type	Primary

End point timeframe:

On day 1 (visit 2, baseline) and day 85 (end of trial)

End point values	2 mg BI 425809	5 mg BI 425809	10 mg BI 425809	25 mg BI 425809
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	121	120	121	119
Units: score on a scale				
arithmetic mean (standard deviation)	0.026 (± 4.864)	0.175 (± 4.471)	0.699 (± 4.313)	-0.174 (± 4.044)

End point values	Placebo group			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: score on a scale				
arithmetic mean (standard deviation)	0.138 (± 4.939)			

Statistical analyses

Statistical analysis title	MCPMod Beta model fit

Statistical analysis description:

Multiple comparison procedures and modelling (MCPmod) techniques for mixed model repeated

measures (MMRM) was used.

Comparison groups	2 mg BI 425809 v 5 mg BI 425809 v 10 mg BI 425809 v 25 mg BI 425809 v Placebo group
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.9931 [2]
Method	MCPMod Beta model fit.

Notes:

[1] - Model assumption: 75% of max effect is achieved at 2 mg, 87.5% at 5 mg, 25% at 25 mg, max effect achieved at 10 mg of BI 425809, scalar parameter = 26

[2] - An alpha of 0.05 was used for one-sided test. The MCPMod procedure adjusts for multiplicity.

Statistical analysis title	MCPMod Emax model fit

Statistical analysis description:

Multiple comparison procedures and modelling (MCPmod) techniques for mixed model repeated measures (MMRM) was used.

Comparison groups	2 mg BI 425809 v 5 mg BI 425809 v 10 mg BI 425809 v 25 mg BI 425809 v Placebo group
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.9225 [4]
Method	MCPMod Emax model fit.

Notes:

[3] - Model assumption: 20% of the maximum effect is achieved at 2 mg

[4] - An alpha of 0.05 was used for one-sided test. The MCPMod procedure adjusts for multiplicity.

Statistical analysis title	MCPMod Sigmoidal Emax model fit

Statistical analysis description:

Multiple comparison procedures and modelling (MCPmod) techniques for mixed model repeated measures (MMRM) was used.

Comparison groups	2 mg BI 425809 v 5 mg BI 425809 v 10 mg BI 425809 v 25 mg BI 425809 v Placebo group
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.9287 [6]
Method	MCPMod Sigmoidal Emax model fit.

Notes:

[5] - Model assumption: 25% of max effect achieved at 5 mg and 75% of max effect achieved at 10 mg of BI 425809

[6] - An alpha of 0.05 was used for one-sided test. The MCPMod procedure adjusts for multiplicity.

Statistical analysis title	MCPMod linear model fit

Statistical analysis description:

Multiple comparison procedures and modelling (MCPmod) techniques for mixed model repeated measures (MMRM) was used.

Comparison groups	2 mg BI 425809 v 5 mg BI 425809 v 10 mg BI 425809 v 25 mg BI 425809 v Placebo group
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.7646 [8]
Method	MCPMod linear model fit.

Notes:

[7] - No assumption needed

[8] - An alpha of 0.05 was used for one-sided test. The MCPMod procedure adjusts for multiplicity.

Statistical analysis title	MCPMod linear in log model fit

Statistical analysis description:

Multiple comparison procedures and modelling (MCPmod) techniques for mixed model repeated measures (MMRM) was used.

Comparison groups	2 mg BI 425809 v 5 mg BI 425809 v 10 mg BI 425809 v 25 mg BI 425809 v Placebo group
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.9335 [10]
Method	MCPMod linear in log model fit.

Notes:

[9] - No assumption needed

[10] - An alpha of 0.05 was used for one-sided test. The MCPMod procedure adjusts for multiplicity.

Statistical analysis title	MCPMod logistic model fit

Statistical analysis description:

Multiple comparison procedures and modelling (MCPmod) techniques for mixed model repeated measures (MMRM) was used.

Comparison groups	2 mg BI 425809 v 5 mg BI 425809 v 10 mg BI 425809 v 25 mg BI 425809 v Placebo group
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.8199 [12]
Method	MCPMod logistic model fit.

Notes:

[11] - Model assumption: 10% of max effect achieved at 5 mg and 50% of max effect achieved at 10 mg of BI 425809

[12] - An alpha of 0.05 was used for one-sided test. The MCPMod procedure adjusts for multiplicity.

Statistical analysis title	Mixed model repeated measures (MMRM)

Statistical analysis description:

MMRM is descripted is in the description section.

Comparison groups	2 mg BI 425809 v Placebo group
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.934 [13]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	1.18
Variability estimate	Standard error of the mean
Dispersion value	0.58

Notes:
[13] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Mixed model repeated measures (MMRM)
Statistical analysis description:	
MMRM is descripted is in the description section.	
Comparison groups	5 mg BI 425809 v Placebo group
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6041 [14]
Method	MMRM
Parameter estimate	Median difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	0.58

Notes:
[14] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Mixed model repeated measures (MMRM)
Statistical analysis description:	
MMRM is described in the description section.	
Comparison groups	10 mg BI 425809 v Placebo group
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1926 [15]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	0.58

Notes:
[15] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Mixed model repeated measures (MMRM)
Statistical analysis description:	
MMRM is described in the description section.	
Comparison groups	25 mg BI 425809 v Placebo group
Number of subjects included in analysis	237

Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9739 [16]
Method	MMRM
Parameter estimate	Median difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	1.12
Variability estimate	Standard error of the mean
Dispersion value	0.58

Notes:

[16] - p-values are nominal without multiplicity adjustment.

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

End point title	Change from baseline in the ADCS-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living) score after 12 weeks of treatment

End point description:

Change from baseline in the ADCS-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living) score after 12 weeks of treatment is presented.

The 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. The sum score could range from 0 to 78, with higher scores indicating less severe impairment. A positive change indicates an improvement from baseline.

Full analysis set (FAS): all randomised patients who were treated with at least one dose of trial medication and had a baseline and at least one corresponding post-baseline on-treatment efficacy assessment for any efficacy endpoint. FAS was used for efficacy analyses.

End point type	Secondary

End point timeframe:

On day 1 (visit 2, baseline) and day 85 (end of trial)

End point values	2 mg BI 425809	5 mg BI 425809	10 mg BI 425809	25 mg BI 425809
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	113	111	110	116
Units: score on a scale				
arithmetic mean (standard deviation)	0.283 (± 6.805)	0.577 (± 5.852)	-1.145 (± 4.764)	-1.828 (± 7.034)

End point values	Placebo group			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: score on a scale				

arithmetic mean (standard deviation)	0.261 (± 4.842)			

Statistical analyses

Statistical analysis title	Analysis of Covariance (ANCOVA)
Statistical analysis description:	
Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.	
Comparison groups	2 mg BI 425809 v Placebo group
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.979 [17]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	1.52
Variability estimate	Standard error of the mean
Dispersion value	0.76

Notes:

[17] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Analysis of Covariance (ANCOVA)
Statistical analysis description:	
Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.	
Comparison groups	5 mg BI 425809 v Placebo group
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.521 [18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0.77

Notes:

[18] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Analysis of Covariance (ANCOVA)

Statistical analysis description:

Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.

Comparison groups	10 mg BI 425809 v Placebo group
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.047 [19]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.77

Notes:

[19] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Analysis of Covariance (ANCOVA)

Statistical analysis description:

Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.

Comparison groups	25 mg BI 425809 v Placebo group
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [20]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.65
upper limit	-0.67
Variability estimate	Standard error of the mean
Dispersion value	0.76

Notes:

[20] - p-values are nominal without multiplicity adjustment.

Secondary: Clinician's Interview-Based Impression of Change (CIBIC+) score after 12 weeks of treatment

End point title	Clinician's Interview-Based Impression of Change (CIBIC+) score after 12 weeks of treatment

End point description:

Clinician's Interview-Based Impression of Change (CIBIC+) score after 12 weeks of treatment is presented.

Clinician's Interview-Based Impression of Change (CIBIC+) and Clinical Interview-Based Impression of Severity (CIBIS) scales are based on semi-structured interview covering domains of function and cognition. They additionally require the assessment of psychiatric signs and symptoms. The patient and their caregiver are interviewed and questioned by the clinician. Change rate is based on an unanchored 7-point scale (scores 1, 2 and 3 = improvement, 4 = no change, 5, 6 and 7 = deterioration).

Full analysis set (FAS): all randomised patients who were treated with at least one dose of trial medication and had a baseline and at least one corresponding post-baseline on-treatment efficacy assessment for any efficacy endpoint. FAS was used for efficacy analyses.

End point type	Secondary

End point timeframe:

On day 1 (visit 2, baseline) and day 85 (end of trial)

End point values	2 mg BI 425809	5 mg BI 425809	10 mg BI 425809	25 mg BI 425809
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	114	112	110	116
Units: score on a scale				
arithmetic mean (standard deviation)	4.000 (± 0.941)	4.080 (± 0.773)	4.209 (± 0.679)	4.224 (± 0.781)

End point values	Placebo group			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: score on a scale				
arithmetic mean (standard deviation)	4.080 (± 0.829)			

Statistical analyses

Statistical analysis title	Analysis of Covariance (ANCOVA)

Statistical analysis description:

Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.

Comparison groups	2 mg BI 425809 v Placebo group
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.343 [22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %

sides	2-sided
lower limit	-0.32
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[21] - Mini Mental State Examination (MMSE)

[22] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Analysis of Covariance (ANCOVA)

Statistical analysis description:

Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.

Comparison groups	5 mg BI 425809 v Placebo group
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.645 [23]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[23] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Analysis of Covariance (ANCOVA)

Statistical analysis description:

Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.

Comparison groups	10 mg BI 425809 v Placebo group
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.448 [24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[24] - p-values are nominal without multiplicity adjustment.

Statistical analysis title	Analysis of Covariance (ANCOVA)

Statistical analysis description:

Analysis of Covariance model included baseline value for the secondary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.

Comparison groups	25 mg BI 425809 v Placebo group
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.34 [25]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.32
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[25] - p-values are nominal without multiplicity adjustment.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until end of treatment + 28 days of follow-up, up to 16 weeks.

Adverse event reporting additional description:

Treated set (TS): the TS included all patients treated with at least one dose of trial medication. Patients in the treated set were analysed based on the actual treatment received at the randomisation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	BI 5mg BI 425809

Reporting group description:

Participants in dose group 2 were orally administered 1 tablet of 5 mg of BI 425809 together with 1 tablet of 1 mg / 5 mg and 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	BI 2mg BI 425809

Reporting group description:

Participants in dose group 1 were orally administered 2 tablets of 1 milligrams (mg) of BI 425809 (Total: 2 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	BI 25mg BI 425809

Reporting group description:

Participants in dose group 4 were orally administered 1 tablet of 25 mg of BI 425809 together with 2 tablets of 1 mg / 5 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	Placebo group

Reporting group description:

Participants in the placebo group were orally administered 2 tablets of 1 mg / 5 mg and 1 tablet of 25 mg of placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Reporting group title	BI 10mg BI 425809

Reporting group description:

Participants in dose group 3 were orally administered 2 tablets of 5 mg of BI 425809 (Total: 10 mg) together with 1 tablet of 25 mg placebo match once daily (qd) during 12 weeks. The tablets were to be taken with water in the morning at approximately the same time every day with or without food.

Serious adverse events	BI 5mg BI 425809	BI 2mg BI 425809	BI 25mg BI 425809
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 122 (3.28%)	5 / 123 (4.07%)	4 / 123 (3.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 122 (0.82%)	2 / 123 (1.63%)	1 / 123 (0.81%)

occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neoplasm			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	0 / 123 (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
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	0 / 123 (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			
Respiratory distress			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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			
Dementia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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
Syncope			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	0 / 123 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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
Glaucoma			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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			
Depression			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	0 / 123 (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			
Pancreatitis acute			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	0 / 123 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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
Musculoskeletal and connective tissue disorders			

Torticollis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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			
Bronchitis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	0 / 123 (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
Gingivitis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 123 (0.81%)	0 / 123 (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
Sepsis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 123 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 122 (0.82%)	0 / 123 (0.00%)	0 / 123 (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

Serious adverse events	Placebo group	BI 10mg BI 425809	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 120 (4.17%)	4 / 122 (3.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neoplasm			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 120 (0.83%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Dementia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 120 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 120 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	1 / 120 (0.83%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 120 (0.83%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Torticollis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 122 (0.82%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BI 5mg BI 425809	BI 2mg BI 425809	BI 25mg BI 425809
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 122 (18.03%)	17 / 123 (13.82%)	19 / 123 (15.45%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 122 (7.38%)	4 / 123 (3.25%)	6 / 123 (4.88%)
occurrences (all)	11	5	8
Headache			
subjects affected / exposed	10 / 122 (8.20%)	6 / 123 (4.88%)	5 / 123 (4.07%)
occurrences (all)	12	7	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 122 (0.82%)	6 / 123 (4.88%)	8 / 123 (6.50%)
occurrences (all)	1	8	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 122 (5.74%)	3 / 123 (2.44%)	3 / 123 (2.44%)
occurrences (all)	9	4	3

Non-serious adverse events	Placebo group	BI 10mg BI 425809	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 120 (10.00%)	14 / 122 (11.48%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 120 (1.67%)	3 / 122 (2.46%)	
occurrences (all)	4	3	
Headache			
subjects affected / exposed	5 / 120 (4.17%)	7 / 122 (5.74%)	

occurrences (all)	6	7	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 120 (1.67%)	2 / 122 (1.64%)	
occurrences (all)	2	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 120 (2.50%)	3 / 122 (2.46%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2017	The amendment introduced a new concept to detect efficacy signals in executive function and memory of the heterogeneous AD patient population in this trial. This included the deletion of the CDR from the main inclusion criteria, a change from ADAS-Cog13 to ADAS-Cog11 as primary endpoint, the deletion of CDR-SB (Clinical Dementia Rating Sum of Boxes) from the secondary endpoints, and the addition CIBIC+ as secondary endpoints and further cognitive tests (COWAT, VFT; Coding and Digit span). Lower Hb levels were allowed per inclusion criteria. The possibility to introduce Vitamin B12 and folate treatments was introduced if values were found below lower limit of normal at Visit 1. The Amendment added Visit 0 to allow comfortable time window for imaging, review of inclusion and exclusion criteria, and concomitant medications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 September 2016	Following the identification of a new major metabolite, BI 761036, BI communicated a voluntary hold of the Phase II to relevant competent authorities on 16 Sep 2016, which was formalised as full clinical hold by FDA on 26 Oct 2016. The clinical hold was removed by FDA on 21 Nov 2017 and the trial was re-initiated.	21 November 2017

Notes:

Limitations and caveats

None reported