Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI proprietary name: Not applicable		**EudraCT number:** 2013-005040-28	
BI investigational product: BI 409306		**Page:** 1 of 6	
Report date: 11 Jun 2018	**Trial no./Doc. no.:** 1289.7/ c22465310-01	**Dates of trial:** 02 Mar 2015 – 10 Oct 2017	**Date of revision:** Not applicable

Title of trial

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

Lay title

A study to test whether BI 409306 improves mental abilities in patients with mild Alzheimer's disease and difficulties with mental functioning

Coordinating investigator

Prof [redacted] France

Trial sites with randomised patients

Multinational trial in 54 sites in 11 countries in Europe and North America

Publications

Data from this trial have not been published at the time of clinical trial report preparation.

Clinical phase: II

Objectives

To assess safety, tolerability and efficacy of different doses of BI 409306 compared to placebo in treatment of cognitive impairment due to Alzheimer's disease (AD)

Methodology

Randomised, double dummy placebo-controlled, double-blind, parallel-design comparison of 5 groups over 12 weeks of treatment.

Number of patients

Planned:	Randomised: 354
Actual:	Screened: 577
	Randomised: 329

Report date:	**Trial no./Doc. no.:**	**Page:**	**Date of revision:**
11 Jun 2018	1289.7/ c22465310-01	2 of 6	Not applicable

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10 mg BI 409306 QD:

Randomised: 55 Treated: 55 Analysed (for primary endpoint): 47

25 mg BI 409306 QD:

Randomised: 53 Treated: 53 Analysed (for primary endpoint): 44

50 mg BI 409306 QD:

Randomised: 55 Treated: 55 Analysed (for primary endpoint): 51

25 mg BI 409306 BID:

Randomised: 55 Treated: 55 Analysed (for primary endpoint): 45

Placebo

Randomised: 106 Treated: 106 Analysed (for primary endpoint): 83

Donepezil:

The donepezil arm was dropped from the trial with CTP Amendment 2, therefore no further patients were randomised to the donepezil arm, but patients already randomised to donepezil continued in the trial as originally planned.

Randomised: 5 Treated: 5 Analysed (for primary endpoint): 0

Diagnosis

Patients with diagnosis of mild Alzheimer's disease according to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.

Main criteria for inclusion

The trial included male and female patients at least 55 years old with mild Alzheimer's disease. A MMSE (Mini-Mental-State-Examination) score between 18-26, an Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog_{11}) score higher than 12 at screening, and a global Clinical Dementia Rating Scale (CDR) score of 1 or greater were required for inclusion. A caregiver had to be available for study site activities and on call by arrangement with the study site.

BI investigational product: BI 409306, tablet

Dose: 10 mg QD, 25 mg QD, 50 mg QD, 25 mg BID

Mode of administration: Oral

Comparator product: Placebo, tablet

Dose: Not applicable

Mode of administration: Oral

Comparator product: Donepezil, tablet

Dose: 5 mg (Weeks 1-4), 10 mg (Weeks 5-12)

Mode of administration: Oral

Duration of treatment

2 to 3 weeks of placebo run-in treatment followed by 12 weeks of randomised treatment

Report date:	Trial no./Doc. no.:	Page:	Date of revision:
11 Jun 2018	1289.7/ c22465310-01	3 of 6	Not applicable

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Efficacy criteria for evaluation

Primary endpoint

Change from baseline in Neuropsychological Test Battery (NTB) total z-score after 12-week treatment.

Secondary endpoints

- Change from baseline in ADCS-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living) total score after 12-week treatment
- Change from baseline in CDR-SB (Clinical Dementia Rating Scale-Sum of Boxes) total score after 12-week treatment
- Change from baseline in ADAS-Cog_{11} (Alzheimer's Disease Assessment Scale-cognitive subscale) total score after 12-week treatment

Safety criteria for evaluation

Adverse event reporting, vital signs, ECG (digital) and standard laboratory tests, physical examination, neurological examination, and Columbia-Suicide Severity Rating Scale (C-SSRS).

Statistical methods

For the primary endpoint analysis, a Restricted Maximum Likelihood Estimation based Mixed-effects Model for Repeated Measures (MMRM) was used to obtain adjusted means for the treatment effects. This model included fixed, categorical effects of treatment, visit, current use of acetylcholinesterase inhibitors (AChEI; Yes, No) and treatment-by-visit interaction, as well as continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was considered as random effect. The unstructured covariance structure was used as covariance structure for within-patient variation.

For the secondary endpoints ADCS-ADL and ADAS-Cog_{11}, an analysis of covariance (ANCOVA) was used to assess the treatment difference between BI 409306 groups and placebo. 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. For the secondary endpoint CDR-SB, the primary endpoint analysis model was applied.

Descriptive statistics.

No formal interim analyses of safety and efficacy data were planned or conducted.

SUMMARY - CONCLUSIONS

Trial patients and compliance with the clinical trial protocol

Overall, 577 patients were enrolled into this trial. Of those, 351 patients started the placebo run-in period and 329 patients were randomised and treated. The overall disposition of patients in the trial was comparable across the treatment groups. Of the treated patients, 92.7% completed the treatment period as planned while 7.3% prematurely discontinued from trial medication. The majority of discontinuations were due to withdrawal of informed consent (not due to an AE; 3.6%) and AEs (2.4%). This was comparable across the treatment groups.

There were 5 patients who were randomised to treatment with donepezil. With CTP Amendment 2, the donepezil arm was dropped from the trial. Therefore no further patients were randomised to the donepezil arm, but patients already randomised to donepezil continued in the trial as originally planned.

Report date:	**Trial no./Doc. no.:**	**Page:**	**Date of revision:**
11 Jun 2018	1289.7/ c22465310-01	4 of 6	Not applicable

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There were 35.6% of patients with IPVs not related to the primary endpoint. The IPVs with an overall frequency >5% were: C-SSRS not administered at every visit (12.2%), use of prohibited concomitant medication before start of the treatment period (9.4%), and use of prohibited medication during the trial (6.1%). IPVs related to the primary endpoint were all connected to an incorrect timing of endpoint measurements (51.4% of patients): assessment of the NTB not done at a similar time across visits (35.6%), NTB not administered by the same rater (16.1%), and recommended assessment order not followed (14.9%). The high number of IPVs related to the primary endpoint shows that it was difficult to adhere to the protocol-specified time windows and the sequence of neuropsychological assessments. Nevertheless, these IPVs were not considered to have a relevant influence on the primary endpoint results.

Demographic data in the trial were generally balanced across the treatment groups and consistent with the planned patient population. The mean patient age was 74.0 years (SD 7.9) and most patients were 65 years or older (86.3%). Patients were predominantly White (98.5%) and gender was evenly distributed (50.5% male and 49.5% female). Most patients were from Europe (78.1%) and not of Hispanic or Latino ethnicity (96.0%).

The mean time since the first onset of symptoms or the diagnosis was 1.46 years (SD 1.73). Overall, 25.2% of patients had a family history of AD in a first degree relative. Pharmacogenomic analysis of CYP2C19 variants showed that 2.4% were poor metabolisers. Overall, 45.3% of patients carried the APOE e4 allele.

In total, the mean duration of exposure to trial medication was 81.5 days (SD 15.4). The mean treatment duration was comparable across treatment groups.

Efficacy results

The adjusted mean change from baseline in NTB z-score was 0.12 (SE 0.030) in the pooled BI 409306 group and 0.15 (SE 0.045) in the placebo group. MMRM treatment comparisons of both groups did not show a significant treatment difference, with an adjusted mean of -0.03 (95% confidence interval -0.135, 0.074, p = 0.5687). No dose-response relationship and no dose group with a peak response could be determined (Table 1).

Table 1 Treatment comparison of change from baseline in mean NTB z-score − FAS

	BI 409306				
	10 mg QD	25 mg QD	50 mg QD	25 mg BID	Placebo
Analysed patients, N	47	44	51	45	83
Mean baseline z-score (SD)	0.03 (0.646)	-0.20 (0.551)	0.02 (0.655)	0.08 (0.673)	0.01 (0.643)
Adjusted mean change (SE)	0.13 (0.059)	0.17 (0.061)	0.16 (0.056)	0.01 (0.060)	0.15 (0.045)
Adjusted mean difference (SE)	-0.02 (0.073)	0.02 (0.075)	0.01 (0.071)	-0.14 (0.074)	
95% confidence interval	(-0.163, 0.124)	(-0.125, 0.171)	(-0.130, 0.152)	(-0.285, 0.006)	
p-value	0.7907	0.7622	0.8789	0.0609	

For the secondary endpoints, analysis of the change from baseline in the mean questionnaire scores showed no consistent statistical separation from placebo in favour of BI 409306 (Table 2).

Report date:	**Trial no./Doc. no.:**	**Page:**	**Date of revision:**
11 Jun 2018	1289.7/ c22465310-01	5 of 6	Not applicable

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Table 2 Treatment comparisons of change from baseline for secondary endpoints − FAS

	BI 409306				
	10 mg QD	25 mg QD	50 mg QD	25 mg BID	Placebo
ADCS-ADL score					
Analysed patients, N	47	43	48	47	84
Mean baseline score (SD)	62.38 (9.061)	62.39 (10.570)	63.29 (9.188)	59.97 (9.720)	61.20 (10.270)
Adjusted mean change (SE)	0.10 (0.853)	-0.99 (0.892)	0.35 (0.847)	-1.07 (0.855)	-0.58 (0.639)
Adjusted mean difference (SE)	0.67 (1.066)	-0.41 (1.099)	0.93 (1.064)	-0.49 (1.066)	
95% confidence interval	(-1.43, 2.77)	(-2.57, 1.76)	(-1.16, 3.03)	(-2.59, 1.61)	
p-value	0.5287	0.7105	0.3822	0.6472	
CDR-SB score					
Analysed patients, N	44	45	52	48	88
Mean baseline score (SD)	5.6 (1.78)	5.9 (1.69)	5.5 (1.96)	6.2 (2.53)	5.6 (1.82)
Adjusted mean change (SE)	0.1 (0.23)	0.3 (0.23)	0.1 (0.21)	0.2 (0.22)	0.1 (0.16)
Adjusted mean difference (SE)	0.1 (0.28)	0.3 (0.28)	0.1 (0.27)	0.1 (0.28)	
95% confidence interval	(-0.46, 0.64)	(-0.29, 0.80)	(-0.45, 0.60)	(-0.43, 0.65)	
p-value	0.7551	0.3643	0.7822	0.6889	
ADAS-Cog$_{11}$ score					
Analysed patients, N	51	46	50	50	86
Mean baseline score (SD)	19.44 (7.126)	20.97 (7.584)	19.62 (7.792)	22.23 (8.366)	21.36 (8.081)
Adjusted mean change (SE)	1.14 (0.738)	0.94 (0.776)	1.11 (0.746)	2.29 (0.746)	-0.18 (0.568)
Adjusted mean difference (SE)	1.32 (0.933)	1.12 (0.962)	1.28 (0.940)	2.47 (0.936)	
95% confidence interval	(-0.52, 3.15)	(-0.77, 3.01)	(-0.57, 3.13)	(0.63, 4.31)	
p-value	0.1595	0.2455	0.1732	0.0088	

Safety results

Overall, 42.6% of patients reported at least 1 AE (Table 3). The most frequently reported AEs with an overall frequency ≥5% at SOC level were 'nervous system disorders' (11.2%), 'infections and infestations' (9.1%), psychiatric disorders (7.9%), gastrointestinal disorders (6.7%), and 'musculoskeletal and connective tissue disorders' (5.8%). At PT level, AEs with an overall frequency ≥2% were headache (4.3%), nasopharyngitis (2.7%), fatigue (2.1%), and dizziness (2.1%). Most reported AEs were of mild or moderate intensity. In total, 5 patients (1.5%) were reported with at least 1 AE of severe intensity.

Adverse events leading to treatment discontinuation were reported for 8 patients (2.4%). The most frequently reported SOC was 'nervous system disorders' (5 patients, 1.5%). Overall, 29 patients (8.8%) were reported with investigator-defined drug-related AEs. At PT level, the only events with an overall frequency >0.5% were photopsia (0.9%), blurred vision (0.9%), headache (0.6%), and dizziness (0.6%). No CTP-prespecified AESIs of hepatic injury were reported.

There was 1 patient who died due the AEs worsening of Alzheimer's disease and progressive encephalopathy. These AEs were not considered drug-related by the investigator. In total, 16 patients (4.9%) were reported with at least 1 serious AE. At PT level, the only serious event with an overall frequency >0.5% was 'suicidal ideation' (0.9%). In total, 6 patients (1.8%) reported suicidal ideations of Grade 1 to 3, i.e. without intent to act.

Report date:	**Trial no./Doc. no.:**	**Page:**	**Date of revision:**
11 Jun 2018	1289.7/ c22465310-01	6 of 6	Not applicable

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There were no clinically relevant changes from baseline for any of the safety laboratory parameters or of vital signs. None of the patients in this trial were potential Hy's law cases.

Table 3 Adverse event overall summary, N (%) – Treated set

	BI 409306						
	10 mg QD	25 mg QD	50 mg QD	25 mg BID	Placebo	Donepezil QD	Total
Number of patients	55 (100.0)	53 (100.0)	55 (100.0)	55 (100.0)	106 (100.0)	5 (100.0)	329 (100.0)
Patients with any AE	22 (40.0)	17 (32.1)	31 (56.4)	24 (43.6)	45 (42.5)	1 (20.0)	140 (42.6)
Severe AEs	2 (3.6)	1 (1.9)	1 (1.8)	0	1 (0.9)	0	5 (1.5)
Investigator-defined drug-related AEs	4 (7.3)	4 (7.5)	7 (12.7)	7 (12.7)	7 (6.6)	0	29 (8.8)
AEs leading to discontinuation of trial medication	1 (1.8)	1 (1.9)	1 (1.8)	1 (1.8)	4 (3.8)	0	8 (2.4)
AEs of special interest	0	0	0	0	0	0	0
Serious AEs	1 (1.8)	3 (5.7)	1 (1.8)	3 (5.5)	8 (7.5)	0	16 (4.9)
Fatal	1 (1.8)	0	0	0	0	0	1 (0.3)
Immediately life-threatening	0	0	1 (1.8)	0	0	0	1 (0.3)
Disability/incapacity	0	0	0	0	0	0	0
Requiring or prolonging hospitalisation	1 (1.8)	2 (3.8)	0	3 (5.5)	6 (5.7)	0	12 (3.6)
Congenital Anomaly or Birth Defect	0	0	0	0	0	0	0
Other	0	1 (1.9)	0	1 (1.8)	2 (1.9)	0	4 (1.2)
Other significant AEs (according to ICH E3)	0	0	0	0	3 (2.8)	0	3 (0.9)

Patients could be counted in more than 1 seriousness criterion.

Conclusions

In this trial, treatment with BI 409306 did not show a consistent statistical separation from placebo for NTB response as well as ADCS-ADL, CDR-SB, and ADAS-Cog_{11} questionnaires. All treatments were generally well tolerated and no safety concerns were identified in the trial.