



Clinical trial results:

A randomised, double-masked, placebo-controlled exploratory study to evaluate pharmacodynamics, safety, and tolerability of orally administered BI 1026706 for 12 weeks in patients with mild visual impairment due to centre-involved diabetic macular oedema (DME)

Summary

EudraCT number	2015-003529-33
Trial protocol	DE HU GB GR ES BE PT
Global end of trial date	24 October 2017

Results information

Result version number	v1 (current)
This version publication date	20 October 2018
First version publication date	20 October 2018

Trial information

Trial identification

Sponsor protocol code	1320.22
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02732951
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	05 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 October 2017
Global end of trial reached?	Yes
Global end of trial date	24 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial investigated the mechanism and the pharmacodynamics of orally administered BI 1026706 (100 milligram (gm) twice daily (bid)) in the treatment of patients with mild vision impairment due to centre-involved DME.

Protection of trial subjects:

As per judgment of the investigator, rescue medication was administered in case of clinically significant worsening of the disease, and could be considered in the event of vision loss of ≥ 5 letters or in the event of Central subfield foveal thickness (CSFT) increase of $\geq 10\%$ as compared with the previous visit confirmed by the Central Reading Centre (CRC). Data obtained after the start of rescue medication were excluded from the primary analysis of the primary endpoint.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2017
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	Belgium: 10
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Portugal: 27
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	169
EEA total number of subjects	169

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)	91
From 65 to 84 years	75
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This was randomised, double-blind, placebo-controlled, parallel-group trial to evaluate pharmacodynamics, safety and tolerability of orally administered Boehringer Ingelheim (BI) 1026706 for 12 weeks in patients with Diabetic Macular Oedema (DME). Of the 169 enrolled patients, 105 were randomised.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended specialist sites which would then ensure that all patients met all inclusion/exclusion criteria. Patients were not to be randomized to trial treatment if any one of the specific entry criteria were violated.

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	Investigator, Monitor, Data analyst, Assessor, Subject

Blinding implementation details:

This was a double-blind trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo matching to BI 1026706

Arm description:

Patients were administered film-coated tablet of placebo to match 100 mg BI 1026706 twice daily orally for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were administered film-coated tablet of placebo to match 100 mg BI 1026706 twice daily orally for 12 weeks.

Arm title	BI 1026706
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Arm description:

Patients were administered film-coated tablet of 100 mg BI 1026706 twice daily orally for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BI 1026706
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were administered film-coated tablet of 100 mg BI 1026706 twice daily orally for 12 weeks.

Number of subjects in period 1^[1]	Placebo matching to BI 1026706	BI 1026706
Started	53	52
Completed	48	46
Not completed	5	6
Adverse event, non-fatal	4	4
Lost to follow-up	-	1
Other than listed	1	-
Protocol deviation	-	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	Placebo matching to BI 1026706
Reporting group description:	
Patients were administered film-coated tablet of placebo to match 100 mg BI 1026706 twice daily orally for 12 weeks.	
Reporting group title	BI 1026706
Reporting group description:	
Patients were administered film-coated tablet of 100 mg BI 1026706 twice daily orally for 12 weeks.	

Reporting group values	Placebo matching to BI 1026706	BI 1026706	Total
Number of subjects	53	52	105
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS): TS includes all patients who were treated with at least 1 dose of trial drug, either BI 1026706 or placebo.			
Units: years			
arithmetic mean	62.2	63.9	
standard deviation	± 9.7	± 8.7	-
Sex: Female, Male			
Treated set (TS): TS includes all patients who were treated with at least 1 dose of trial drug, either BI 1026706 or placebo.			
Units: Subjects			
Female	14	14	28
Male	39	38	77
Race (NIH/OMB)			
Treated set (TS): TS includes all patients who were treated with at least 1 dose of trial drug, either BI 1026706 or placebo.			
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	38	47	85
More than one race	0	0	0
Unknown or Not Reported	14	5	19
Ethnicity (NIH/OMB)			
Treated set (TS): TS includes all patients who were treated with at least 1 dose of trial drug, either BI 1026706 or placebo.			
Units: Subjects			
Hispanic or Latino	4	4	8
Not Hispanic or Latino	35	43	78
Unknown or Not Reported	14	5	19

End points

End points reporting groups

Reporting group title	Placebo matching to BI 1026706
Reporting group description: Patients were administered film-coated tablet of placebo to match 100 mg BI 1026706 twice daily orally for 12 weeks.	
Reporting group title	BI 1026706
Reporting group description: Patients were administered film-coated tablet of 100 mg BI 1026706 twice daily orally for 12 weeks.	

Primary: Change from baseline in Central Subfield Foveal Thickness (CSFT) at Week 12

End point title	Change from baseline in Central Subfield Foveal Thickness (CSFT) at Week 12
End point description: The change from baseline in CSFT at Week 12 and the BI 1026706 effect was compared between the BI 1026706 treatment group and the placebo group as measured by Spectral-domain Optical Coherence Tomography (SD-OCT). Baseline was defined as the CSFT value measured at the visit when patients were randomised. Mean presented here is an adjusted mean. Full analysis set (FAS): FAS includes all patients who were randomised, treated with at least 1 dose of BI 1026706 or placebo, and with a baseline and at least one post randomisation central subfield foveal thickness (CSFT) measurement.	
End point type	Primary
End point timeframe: Baseline and Week 12	

End point values	Placebo matching to BI 1026706	BI 1026706		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47 ^[1]	47 ^[2]		
Units: Micrometre [μm]				
arithmetic mean (standard deviation)	-6.19 ($\pm$ 11.61)	10.26 ($\pm$ 11.64)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Null hypothesis = The CSFT change from baseline at Week 12 is equal in both groups	
Comparison groups	BI 1026706 v Placebo matching to BI 1026706

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.3199
Method	Mixed model for repeated measurements
Parameter estimate	Adjusted Mean
Point estimate	16.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.23
upper limit	49.13
Variability estimate	Standard error of the mean
Dispersion value	16.45

Notes:

[3] - Fixed effects of treatment, prior anti-diabetic macular oedema treatment status, visit, treatment by visit interaction, baseline, baseline by visit interaction; patient as a random effect; unstructured covariance matrix for within patient errors. Kenward–Roger approximation was used for denominator degrees of freedom.

Secondary: Number of subjects with serious adverse events (SAEs), Investigator defined drug-related Adverse events (AEs) and adverse events of special interest (AESIs)

End point title	Number of subjects with serious adverse events (SAEs), Investigator defined drug-related Adverse events (AEs) and adverse events of special interest (AESIs)
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End point description:

Number of subjects with serious adverse events (SAEs), Investigator defined drug-related Adverse events (AEs) and adverse events of special interest (AESIs) comparing the BI 1026706 treatment group with the placebo group is presented. Treated set (TS): TS includes all patients who were treated with at least 1 dose of trial drug, either BI 1026706 or placebo.

End point type	Secondary
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End point timeframe:

From first drug administration until 4 days after last drug administration, up to 89 days.

End point values	Placebo matching to BI 1026706	BI 1026706		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53 ^[4]	52 ^[5]		
Units: Count of participants				
Total with SAEs	2	2		
Investigator defined drug-related AE	7	7		
AESIs	0	1		

Notes:

[4] - TS

[5] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 4 days after last drug administration, up to 89 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Placebo matching to BI 1026706
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Reporting group description:

Patients were administered film-coated tablet of placebo to match 100 mg BI 1026706 twice daily orally for 12 weeks.

Reporting group title	BI 1026706
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Reporting group description:

Patients were administered film-coated tablet of 100 mg BI 1026706 twice daily orally for 12 weeks.

Serious adverse events	Placebo matching to BI 1026706	BI 1026706	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)	7 / 52 (13.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell count decreased			

subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glycosuria			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Reactive perforating collagenosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Localised infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo matching to BI 1026706	BI 1026706	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 53 (22.64%)	14 / 52 (26.92%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 53 (5.66%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 53 (1.89%)	4 / 52 (7.69%)	
occurrences (all)	2	7	
Somnolence			
subjects affected / exposed	3 / 53 (5.66%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 53 (7.55%)	6 / 52 (11.54%)	
occurrences (all)	4	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2016	Exclusion Criterion and the numbering of the subsequent exclusion criteria was adjusted. A footnote was added providing further details for this exclusion criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported