Clinical trial results:
A study that tests BI 1467335 in patients with diabetic eye disease (diabetic retinopathy). It looks at the way BI 1467335 is taken up, the effects it has, and how well it is tolerated

Summary

EudraCT number	2016-002971-91
Trial protocol	NO GR GB ES IT PT
Global end of trial date	14 May 2020

Results information

Result version number	v1 (current)
This version publication date	31 May 2021
First version publication date	31 May 2021

Trial information

Trial identification

Sponsor protocol code	1386-0012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03238963
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, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 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	14 July 2020
Is this the analysis of the primary	No

completion data?	
Global end of trial reached?	Yes
Global end of trial date	14 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate safety and tolerability of 12 weeks treatment of oral BI 1467335 compared to placebo in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) without center-involved diabetic macular edema (CI-DME) and secondary to explore the efficacy of BI 1467335 on improvement of diabetic retinopathy.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 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	Austria: 2
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	United States: 213
Worldwide total number of subjects	288
EEA total number of subjects	46

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)	202

From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A study evaluated safety and tolerability of 12-week treatment of oral BI 1467335 compared to placebo in patients with moderately severe to severe non-proliferative diabetic retinopathy without center-involved diabetic macular edema and explored the efficacy of BI 1467335 on improvement of diabetic retinopathy.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the 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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 1467335 10 mg

Arm description:

2 film coated tablets of 5 milligram (mg) BI 1467335 (Total: 10 mg) were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.

Arm type	Experimental
Investigational medicinal product name	BI 1467335
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 film coated tablets of 5 milligram (mg) BI 1467335 (Total: 10 mg) were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.

Arm title	Placebo

Arm description:

2 film coated tablets of matching placebo were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.

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:

2 film coated tablets of matching placebo were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.

Number of subjects in period 1[1]	BI 1467335 10 mg	Placebo
Started	40	39
Completed	35	37
Not completed	5	2
Protocol deviation	1	1
Prohibited medication given due to hospital stay	1	-
Adverse event, non-fatal	1	-
Consent withdrawn by subject	1	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: 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 1467335 10 mg
Reporting group description:	
2 film coated tablets of 5 milligram (mg) BI 1467335 (Total: 10 mg) were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.	
Reporting group title	Placebo
Reporting group description:	
2 film coated tablets of matching placebo were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.	

Reporting group values	BI 1467335 10 mg	Placebo	Total
Number of subjects	40	39	79
Age categorical			
Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).			
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)	33	32	65
From 65-84 years	7	7	14
85 years and over	0	0	0
Age Continuous			
Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).			
Units: years			
arithmetic mean	52.5	53.1	
standard deviation	± 10.8	± 13.3	-
Sex: Female, Male			
Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).			
Units: Participants			
Female	14	14	28
Male	26	25	51
Race (NIH/OMB)			
Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	1	4	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	36	31	67
More than one race	0	0	0

Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).			
Units: Subjects			
Hispanic or Latino	18	15	33
Not Hispanic or Latino	22	24	46
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	BI 1467335 10 mg
Reporting group description:	
2 film coated tablets of 5 milligram (mg) BI 1467335 (Total: 10 mg) were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.	
Reporting group title	Placebo
Reporting group description:	
2 film coated tablets of matching placebo were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.	

Primary: Percentage of participants with any ocular adverse events over the on-treatment period

End point title	Percentage of participants with any ocular adverse events over the on-treatment period[1]
End point description:	
Percentage of participants with any ocular adverse events over the on-treatment period was reported. Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).	
End point type	Primary
End point timeframe:	
On-treatment period: from first dose of study drug until end of follow-up period, up to 24 weeks.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 1467335 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: Percentage of participants				
number (not applicable)	35.0	23.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with at least 2 steps improvement from baseline in the study eye on the Diabetic Retinopathy Severity Scale (DRSS) at week 12

End point title	Percentage of participants with at least 2 steps improvement from baseline in the study eye on the Diabetic Retinopathy Severity Scale (DRSS) at week 12
End point description:	
7-field or modified 4-field digital fundus photographs was obtained from both eyes by a qualified person according to the imaging manual to collect all data for the assessment of the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS). The images was sent to the independent central reading center who performs the grading on the basis of the DRSS. The DRSS	

ranges from level 10 (Diabetic retinopathy absent) to level 85 (advanced proliferative Diabetic retinopathy). Full analysis set (FAS): the FAS consists of all the patients who were randomized, treated with at least one dose of BI 1467335/placebo and have baseline and one on-treatment Diabetic Retinopathy Severity Scale assessment.

End point type	Secondary

End point timeframe:

At baseline and at Week 12.

End point values	BI 1467335 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Percentage of participants				
number (not applicable)	5.7	0.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference of BI 1467335 10 milligram (mg) group minus Placebo group was presented. 95% confidence interval was calculating using the Chan and Zhang method.

Comparison groups	BI 1467335 10 mg v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	
Method	Chan and Zhang method
Parameter estimate	Risk difference (RD)
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.192
Variability estimate	Standard error of the mean
Dispersion value	0.039

Secondary: Percentage of participants with adverse events other than ocular adverse events over on-treatment period

End point title	Percentage of participants with adverse events other than ocular adverse events over on-treatment period

End point description:

Percentage of participants with adverse events other than ocular adverse events over on-treatment period was reported. Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).

End point type	Secondary

End point timeframe:

End point values	BI 1467335 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: Percentage of participants				
number (not applicable)	55.0	82.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until end of follow-up period, up to 24 weeks.

Adverse event reporting additional description:

Treated set (TS): the TS consists of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	BI 1467335 10 mg

Reporting group description:

2 film coated tablets of 5 milligram (mg) BI 1467335 (Total: 10 mg) were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.

Reporting group title	Placebo

Reporting group description:

2 film coated tablets of matching placebo were taken orally once daily for a treatment period of 12 weeks with 12 weeks of follow-up.

Serious adverse events	BI 1467335 10 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 40 (17.50%)	4 / 39 (10.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (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			
Dysarthria			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (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			
Cellulitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BI 1467335 10 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 40 (40.00%)	25 / 39 (64.10%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Blood glucose increased			
subjects affected / exposed	1 / 40 (2.50%)	3 / 39 (7.69%)	
occurrences (all)	1	4	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Lipase increased			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
Glucose urine present			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Protein urine present			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 40 (2.50%)	4 / 39 (10.26%)	
occurrences (all)	1	5	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 40 (17.50%)	5 / 39 (12.82%)	
occurrences (all)	9	6	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	3 / 40 (7.50%)	2 / 39 (5.13%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 40 (5.00%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Nausea			
subjects affected / exposed	2 / 40 (5.00%)	6 / 39 (15.38%)	
occurrences (all)	2	7	
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	4	
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Hypoglycaemia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 40 (5.00%)	5 / 39 (12.82%)	
occurrences (all)	2	5	
Localised infection			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	

Urinary tract infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 39 (5.13%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2018	- Descriptive analysis of the secondary efficacy endpoint was added because the number of patients with at least 2-step improvement in Diabetic retinopathy Screened set (DRSS) by Week 12 could be too small for adequate statistical modelling (which had been planned in the original clinical trial protocol). - Upon request by the health authorities, changes were made to Inclusion Criteria 1 and 3, Exclusion criteria 1 and 15, the rules for withdrawal from trial treatment, and restrictions regarding concomitant treatment were made. Furthermore, rescreening of patients based on the changed inclusion/exclusion criteria was allowed. - Fasting prior to drug administration and prior to study visits was no longer required, as data from trail 1386.17 had shown that Bi 1467335 could be given with or without food.
20 March 2018	- The drug profile, benefit-risk assessment, Exclusion Criterion 7, and restrictions regarding concomitant treatment and diet/life style were updated, as BI 1467335 had been demonstrated in vitro to be an irreversible inhibitor of MAO-B. - Use of the Heidelberg Optical coherence tomography (OCT) device was allowed (as an alternative to the OptoVue device) and the consistent use of the same device by a given patient throughout the trial was emphasized. - The treatment with aflibercept (Eylea®) or ranibizumab (Lucentis®) in the fellow eye was allowed during the trial.
01 August 2018	- It was stated that the screening visit should be split into 2 parts, when possible, to account for the high probability of patients failing screening due to DRSS grading. - Food and diet precautions were modified. - Upon request by the healthy authorities, bupropion, triptans, linezolide, tedizolid, methylene blue, lithium, and pethidine were added as restricted concomitant treatments and a section regarding gamete donation was introduced.
11 April 2019	- The number of pharmacokinetic and pharmacodynamic sampling was reduced in order to reduce the burden on patients. - A sentence describing a potential sensitivity analysis excluding observations obtained after the start of rescue medication was removed, as no such rescue medication had been defined.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported