



Clinical trial results:

A combined Phase IIa / IIb study of the efficacy, safety, and tolerability of repeated topical doses of regorafenib eye drops, in treatment-naïve subjects with neovascular age related macular degeneration

Summary

EudraCT number	2012-003763-22
Trial protocol	HU DE CZ SK
Global end of trial date	17 June 2015

Results information

Result version number	v1
This version publication date	28 June 2016
First version publication date	28 June 2016

Trial information

Trial identification

Sponsor protocol code	BAY73-4506/15984
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02222207
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	17 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective for part A is to assess the effect of treatment with regorafenib eye drops on visual acuity at Study Week 4 and at Study Week 12 in subjects with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Israel: 8
Worldwide total number of subjects	52
EEA total number of subjects	44

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)	7
From 65 to 84 years	38
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 27 centers, between 10 October 2014 (first subject first visit) and 17 June 2015 (last subject last visit).

Pre-assignment

Screening details:

Study was planned to be conducted in 2 parts, Part A and B, in Part A 89 subjects were enrolled, of them 37 were screen failure and 52 were assigned to treatment, 1 subject was excluded from all analysis sets due to protocol deviations and 51 subjects were analyzed. Part B was not initiated and the study terminated following completion of Part A.

Period 1

Period 1 title	Overall Trial
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A Regorafenib
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Arm description:

Subjects self-administered 30 milligram per milliliter (mg/mL), 25 microliter (mcL), 1 drop of Regorafenib eye drops, topically thrice daily (TID) to the study eye for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ocular use

Dosage and administration details:

Self-administration of 30 mg/mL, 25 mcL, 1 drop of Regorafenib eye drops, TID to the study eye for 12 weeks.

Number of subjects in period 1	Part A Regorafenib
Started	52
Treated and valid for Full Analysis Set	51
Completed	48
Not completed	4
Death	1
Other	2
Adverse event	1

Period 2

Period 2 title	Baseline period
Is this the baseline period?	Yes ^[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A Regorafenib
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Arm description:

Subjects self-administered 30 milligram per milliliter (mg/mL), 25 microliter (mcL), 1 drop of Regorafenib eye drops, topically thrice daily (TID) to the study eye for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ocular use

Dosage and administration details:

Self-administration of 30 mg/mL, 25 mcL, 1 drop of Regorafenib eye drops, topically TID to the study eye for 12 weeks.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline data is available only for treated participants and not randomized participants, hence this period has been created to report the baseline data.

Number of subjects in period 2	Part A Regorafenib
Started	51
Completed	51

Baseline characteristics

Reporting groups^[1]

Reporting group title	Part A Regorafenib
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Reporting group description:

Subjects self-administered 30 milligram per milliliter (mg/mL), 25 microliter (mcL), 1 drop of Regorafenib eye drops, topically thrice daily (TID) to the study eye for 12 weeks.

Notes:

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

Justification: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Reporting group values	Part A Regorafenib	Total	
Number of subjects	51	51	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	75 ± 8.4	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	22	22	

End points

End points reporting groups

Reporting group title	Part A Regorafenib
Reporting group description: Subjects self-administered 30 milligram per milliliter (mg/mL), 25 microliter (mcL), 1 drop of Regorafenib eye drops, topically thrice daily (TID) to the study eye for 12 weeks.	
Reporting group title	Part A Regorafenib
Reporting group description: Subjects self-administered 30 milligram per milliliter (mg/mL), 25 microliter (mcL), 1 drop of Regorafenib eye drops, topically thrice daily (TID) to the study eye for 12 weeks.	
Subject analysis set title	Full Analysis Set (FAS-Part A)
Subject analysis set type	Full analysis
Subject analysis set description: FAS (N=51) included subjects who received at least one dose of study medication.	
Subject analysis set title	Safety analysis set (SAF-Part A)
Subject analysis set type	Safety analysis
Subject analysis set description: SAF (N=51) included subjects who received at least one dose of study medication.	

Primary: Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Study Week 4 for Study Part A

End point title	Change From Baseline in Best Corrected Visual Acuity (BCVA) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Study Week 4 for Study Part A ^[1]
End point description: Subjects will be assessed at each clinic visit for best corrected visual acuity using the early treatment diabetic retinopathy study chart. Visual function of the study eye and the fellow eye was assessed using the ETDRS. The subject's ETDRS testing score was recorded in the appropriate eCRF page at each study visit. For patients that dropped out or received rescue treatment the last observation before drop-out or administration of rescue treatment was carried forward.	
End point type	Primary
End point timeframe: Baseline, Week 4	
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: Statistical analysis were provided as an attachment	

End point values	Part A Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[2]			
Units: Score on scale				
arithmetic mean (standard deviation)	1.18 (± 7.55)			

Notes:

[2] - FAS

Attachments (see zip file)	15984_Statistical analysis of change in BCVA in ETDRS letter
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Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in BCVA as Measured by ETDRS Letter Score at Study Week 12 for Study Part A

End point title	Change From Baseline in BCVA as Measured by ETDRS Letter Score at Study Week 12 for Study Part A ^[3]
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End point description:

Subjects were assessed at each clinic visit for best corrected visual acuity using the early treatment diabetic retinopathy study chart. Visual function of the study eye and the fellow eye was assessed using the ETDRS protocol. ETDRS testing score was recorded in the appropriate eCRF page at each study visit. For patients that dropped out or received rescue treatment the last observation before drop-out or administration of rescue treatment was carried forward.

End point type	Primary
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End point timeframe:

Baseline, Week 12

Notes:

[3] - 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: Statistical analysis were provided as an attachment

End point values	Part A Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[4]			
Units: Score on scale				
arithmetic mean (standard deviation)	-2.36 (± 7.68)			

Notes:

[4] - FAS

Attachments (see zip file)	15984_Statistical analysis of change in BCVA in ETDRS letter
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Individual Changes in BCVA of greater than equal to ($\geq$) 0 Letters of Vision From Study Week 4 to Week 12 for Study Part A

End point title	Percentage of Subjects With Individual Changes in BCVA of greater than equal to ($\geq$) 0 Letters of Vision From Study Week 4 to Week 12 for Study Part A
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End point description:

Subjects were assessed at each clinic visit for BCVA using the early treatment diabetic retinopathy study chart. For patients that dropped out or received rescue treatment the last observation before drop-out or administration of rescue treatment was carried forward.

End point type	Secondary
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End point timeframe:

Week 4, Week 12

End point values	Part A Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[5]			
Units: percentage of subjects				
number (not applicable)	42			

Notes:

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Loss in BCVA of ≥ 10 Letters From Baseline to Study Week 12 for Study Part A

End point title	Percentage of Subjects With a Loss in BCVA of ≥ 10 Letters From Baseline to Study Week 12 for Study Part A
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End point description:

Subjects were assessed at each clinic visit for BCVA using the early treatment diabetic retinopathy study chart. For patients that dropped out or received rescue treatment the last observation before drop-out or administration of rescue treatment was carried forward.

End point type	Secondary
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End point timeframe:

Baseline, Week 12

End point values	Part A Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	50 ^[6]			
Units: percentage of subjects				
number (not applicable)	16			

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment until 30 days after last dose of study drug treatment (up to Week 16)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Part A Regorafenib
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Reporting group description:

Subjects self-administered 30 mg/mL, 25 mL, 1 drop of regorafenib eye drops, topically thrice daily (TID) to the study eye for 12 weeks.

Serious adverse events	Part A Regorafenib		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 51 (5.88%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Visual acuity tests abnormal			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Part A Regorafenib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 51 (21.57%)		
Investigations			
Visual acuity tests abnormal			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	6		
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2015	Addition of subfoveal fibrosis in exclusion criteria; Clarification of the exclusion of subjects requiring steroid treatment; Deletion of controlled glaucoma as an exclusion criteria; Inclusion of a description of how ranibizumab will be used.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 June 2015	The study was prematurely terminated since pre-defined proof of concept (PoC) criteria were not met in Part A, hence part B was not initiated.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As the study was prematurely terminated since pre-defined proof of concept (PoC) criteria were not met in Part A, hence part B was not initiated. Part B related end points and data were not reported since it is not conducted.

Notes: