Clinical trial results:
Phase IV study to evaluate genetic variants of VEGF pathway as biomarkers of VEGF Trap-Eye treatment efficacy in subjects with neovascular age-related macular degeneration (wAMD).

Summary

EudraCT number	2013-002124-17
Trial protocol	ES
Global end of trial date	20 December 2017

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	Relationship between Aflibercept Efficacy and Genetic Variants of Genes Associated with Neovascular Age-Related Macular Degeneration: The BIOIMAGE Trial (BIOIMAGE.pdf)

Trial information

Trial identification

Sponsor protocol code	IMO-AFLI-2013-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fundació IMO
Sponsor organisation address	Josep Maria Lladó 3, Barcelona, Spain,
Public contact	Elisabet Molina, Trial Form Support, +34 931850200, elisabet.molina@tfscro.com
Scientific contact	Elisabet Molina, Trial Form Support, +34 931850200, elisabet.molina@tfscro.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	20 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2017
Global end of trial reached?	Yes
Global end of trial date	20 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study genetic variants of VEGF pathway (SNP markers located within the coding and regulatory regions of the genes of the VEGF pathway) and its relation to VEGF trap-Eye treatment efficacy in terms of the percentage of patients with ? 15 letters gain in visual acuity.

Protection of trial subjects:

Patients were treated according to routine clinical practice (phase IV trial). They were informed of all additional tests that had to be performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 January 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	Spain: 193
Worldwide total number of subjects	193
EEA total number of subjects	193

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)	70
From 65 to 84 years	100
85 years and over	24

Subject disposition

Recruitment

Recruitment details:

The investigator had to ensure that all patients who were offered the possibility to participate in the study met the following inclusion criteria and none of the exclusion criteria. In order to ensure that the study population was representative of all eligible patients, the investigator could not apply any additional exclusion criteria.

Pre-assignment

Screening details:

The subjects met all of the following inclusion criteria:
1. Males or females aged 50 or over.
2. Patients with active primary subfoveal CNV (secondary to the AMD), including juxtafoveal lesions affecting the fovea (confirmed through angiography) in the study eye.
3. Patients with a baseline BCVA per ETDRS optotype of 20/40 to 20/320

Pre-assignment period milestones

Number of subjects started	194
Number of subjects completed	194

Period 1

Period 1 title	visual acuity and genetic variations (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

Single arm To identify the genetic variants of the vascular endothelial growth factor (VEGF) pathway genes and other
genes associated with neovascular age-related macular degeneration (nAMD) as possible predictive biomarkers of a
favorable treatment response to aflibercept

Arm type	Tratment according to labelling
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	authorized drug
Other name	Eylea
Pharmaceutical forms	Suspension for injection in pre-filled injector
Routes of administration	Intravitreal use

Dosage and administration details:

Patients were treated with aflibercept 2 mg (40 mg/mL) IVT
during a 52-week study period, receiving 1 IVT injection once
monthly for the first 3 months (loading phase: weeks 0, 4, and 8),
and then 1 IVT injection every 8 weeks (q8) until week 48 (scheduled treatment). All patients concluded the study period at week
52. At week 48, patients were invited to participate in a 52-week
extension phase. In the extension phase, the interval between visits for aflibercept administration was extended by 2 weeks
per visit (in relation to the period since the last visit) to a maximum
of 12 weeks if no evidence of disease activity was observed (treatand-extend regimen). If there were signs of activity, patients were
retreated, and the next visit was reduced by 2 weeks, with a minimum of 8 weeks between visits. Patients concluded the extension
phase after 104 weeks

Number of subjects in period 1	Single arm
Started	194
Completed	170
Not completed	24
Adverse event, serious fatal	4
Adverse event, non-fatal	5
Consent withdrawn by subject	6
other	5
Lost to follow-up	4

Baseline characteristics

Reporting groups	
Reporting group title	visual acuity and genetic variations

Reporting group description: -

Reporting group values	visual acuity and genetic variations	Total	
Number of subjects	194	194	
Age categorical			
People with neovascular age-related macular degeneration			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	70	70	
From 65-84 years	100	100	
85 years and over	24	24	
Gender categorical			
Units: Subjects			
Female	106	106	
Male	87	87	

Subject analysis sets	
Subject analysis set title	genetic variants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

patients included in the trial (n=194) underwent genetic analysis through blood test

Subject analysis set title	visual acuity analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all patients included in the trial (n=194) underwent visual acuity examination

Reporting group values	genetic variants	visual acuity analysis	
Number of subjects	193	193	
Age categorical			
People with neovascular age-related macular degeneration			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		70	
From 65-84 years		100	
85 years and over		24	
Gender categorical Units: Subjects			
Female	106	106	
Male	87	87	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

Single arm To identify the genetic variants of the vascular endothelial growth factor (VEGF) pathway genes and other
genes associated with neovascular age-related macular degeneration (nAMD) as possible predictive biomarkers of a
favorable treatment response to aflibercept

Subject analysis set title	genetic variants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

patients included in the trial (n=194) underwent genetic analysis through blood test

Subject analysis set title	visual acuity analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all patients included in the trial (n=194) underwent visual acuity examination

Primary: to determine genetic variants of VEGF pathway and its correlation with patients who presented an increase in VA of more than 15 letters at week 52

End point title	to determine genetic variants of VEGF pathway and its correlation with patients who presented an increase in VA of more than 15 letters at week 52

End point description:

Multivariate logistic regression revealed significant effect of six SNPs (in six genes) on gaining≥15 letters in BCVA at week 52. Thus, the odds of gaining ≥15 letters in BCVA after 52 weeks of aflibercept treatment were higher in patients with genotypes TT in rs12366035 (VEGFB) (OR=216.9; p<0.001), AA/AG in rs25681 (C5) (OR=19.7/8.3; p<0.001/ 0.01), CT/CC in rs17793056 (CX3CR1) (OR=8.1/6.2; p<0.01/0.05), CC in rs1800775 (CETP) (OR=6.6; p<0.01), GG/AA in rs2069845 (IL6) (OR=5.6/3.3; p<0.05/0.05), and CT in rs13900 (CCL2) (OR=4.0; p<0.01).

End point type	Primary

End point timeframe:

52 weeks

Statistical analyses

Statistical analysis title	correlation between aflibercept and gene variants

Statistical analysis description:

All data were descriptively analysed. Continuous variables were presented with mean and corresponding 95% CI, median, standard deviation
(SD) and range (minimum, maximum) while categorical variables with frequencies and percentages. Differences between categorical variables were analysed with Chi-square or Fisher’s exact tests, as applicable.
For continuous variables, changes from baseline were analysed using Student's t-test for paired data.

Univariate logistic regressions were used to study

Comparison groups	
Number of subjects included in analysis	0
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 5
Method	ANOVA
Parameter estimate	Odds ratio (OR)

Notes:

[1] - correlation analysis within the same study group

Secondary: percentage of patients who presented a gain or loss of more than 15 letters at week 52

End point title	percentage of patients who presented a gain or loss of more than 15 letters at week 52

End point description:

the percentage of patients who gained 15 or more letters at week 52 was 33,0%

End point type	Secondary

End point timeframe:

52 weeks

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 hours for Serious adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	SOC
Dictionary version	27

Reporting groups	
Reporting group title	adverse event reporting

Reporting group description: -

Serious adverse events	adverse event reporting		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 194 (3.09%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Vascular disorders			
peripheral retinal ischemia			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal pigment epithelial tear			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
retinal tear			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Endophthalmitis			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	adverse event reporting		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 194 (43.81%)		
Vascular disorders			
retinal ichemia and neovasciularization			
subjects affected / exposed	6 / 194 (3.09%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences (all)	2		
Investigations			
Ocular hypertension			
subjects affected / exposed	7 / 194 (3.61%)		
occurrences (all)	7		
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	7 / 194 (3.61%)		
occurrences (all)	7		
Uveitis			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences (all)	1		
other eye disorders			
subjects affected / exposed	52 / 194 (26.80%)		
occurrences (all)	52		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	8 / 194 (4.12%)		
occurrences (all)	8		
other ocular infections			
subjects affected / exposed	2 / 194 (1.03%)		

occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2013	included a new participant centre (Hospital de Cruces, Vizcaya) into the study.
03 December 2013	changed the principal investigator in the Hospital Universitario y Politécnico La Fe de Valencia.
17 February 2014	This amendment (17 Feb 2014) modified three different aspects of the protocol. First, the exclusion criteria num 2. "Patients previously treated with anti-VEGF in the study eye" was modified. The following new exclusion criteria was included: "Previous systemic anti-VEGF treatment, approved or experimental, during the three months prior to the first dose of the study is not allowed during the study". Second, the amendment added that during the bimonthly administration phase Clinical Study Report Sponsor: Fundació IMO Version: Final Study Code: IMO-AFLI-2013-01 Date: 20/12/2017 EudraCT No.: 2013-002124-17 Confidential Page 50 of 171 (weeks 16, 24 and 32), patients were allowed to receive unscheduled treatment (never before 4 weeks) if the following rescue criteria were strictly met: Loss of > 5 letters AND Increase of at least 100 micras in retinal thickness attributable to the baseline disease. Third, there were two changes in terms of participant centers: The Fundación Oftalmológica del Mediterráneo (FOM) has changed the name to FISABIO-Oftalmología Médica Dr Mª Isabel López Sánchez will perform the study in the Hospital Clínico Universitario de Valladolid, not in the IOBA center, as initially exposed
15 February 2015	adds the period "treat and extend" by which all patients with a bimonthly regimen with aflibercept the whole first year of treatment (week 48) were included in the study after gave their informed consent
30 September 2015	A change in the principal investigator in The Hospital La Paz was done.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported