



Clinical trial results:

A Randomized, Double-masked, Sham-controlled Phase 4 Study of the Efficacy, Safety, and Tolerability of Intravitreal Aflibercept Monotherapy Compared to Aflibercept With Adjunctive Photodynamic Therapy in patients with Polypoidal Choroidal Vasculopathy (ATLANTIC)

Summary

EudraCT number	2015-001368-20
Trial protocol	PT ES
Global end of trial date	05 September 2018

Results information

Result version number	v1 (current)
This version publication date	27 October 2021
First version publication date	27 October 2021
Summary attachment (see zip file)	StudyReport Synopsis (ATLANTIC_Imp16-7-3_StudyReportSynopsis_01_20191217.pdf)

Trial information

Trial identification

Sponsor protocol code	ECR-AMD-2015-09
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02495181
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIBILI
Sponsor organisation address	Edifício Prof. Doutor José Cunha-Vaz, Azinhaga de Santa Comba, Celas, Coimbra, Portugal, 3000-548
Public contact	Sónia Simões, AIBILI - Association for Innovation and Biomedical Research on Light and Image, atlantic@aibili.pt
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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 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2018
Global end of trial reached?	Yes
Global end of trial date	05 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Aflibercept with and without PDT in AMD patients diagnosed with PCV, by:
1- Comparing best corrected visual acuity (BCVA) changes at Week 52 in AMD patients with PCV treated with Aflibercept associated with verteporfin PDT versus BCVA in AMD patients with PCV treated with Aflibercept associated with sham PDT.

2- Comparing polyps regression at Week 52 in AMD patients with PCV treated with Aflibercept associated with verteporfin PDT versus polyps regression in AMD patients with PCV treated with Aflibercept associated with sham PDT.

Polyps regression has been defined as a reduction in the total area of polyps, as assessed by the Central Reading Centre.

Protection of trial subjects:

This study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite E6 (R2), Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21 and Japanese Ministry of Health, Labor, and Welfare) and with the ethical principles laid down in the Declaration of Helsinki.

The Principal Investigators and all clinical study staff conducted the clinical study in compliance with the protocol. The Principal Investigators ensured that all personnel involved in the conduct of the study were qualified to perform their assigned responsibilities through relevant education, training and experience. Patients only performed any of the study procedures after providing written IRB/IEC approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient or witnessed, where required by law or regulation. In cases where the patient's representative gave consent, the patient has been informed about the study to the extent possible given his/her understanding. If the patient was capable of doing so, he/she indicated assent by personally signing and dating the written informed consent document. The process of obtaining informed consent has been documented in the patient source documents. The Investigator ensured that each patient was fully informed about the nature and objective of the study and possible risks and benefits associated with participation. The Investigator kept in the study investigator file the original of each patient's signed informed consent form and gave a copy to the patient.

Background therapy:

If patient's eligibility was confirmed, patients received one intravitreal injection of Aflibercept, 2 mg, (IVA) per month for three consecutive doses at weeks 0, 4 and 8 (loading phase).

Patients returned for treatment at Week 16 and they were randomized, according to stratification by polyps' activity as indicated by ICGA, (1:1): to one of the following groups,

- Group 1: Intravitreal Injection of Aflibercept 2 mg T&E + Verteporfin PDT
- Group 2: Intravitreal Injection of Aflibercept 2 mg T&E + Sham PDT

Note:

- At Week 16 all patients received IVA. PDT was only applied if presence of active polyps was confirmed on the ICGA.
- The need of PDT was also assessed on Weeks 28 and 40.
- Frequency of IVA was assessed on Weeks 16, 28 and 40.

Evidence for comparator: -

Actual start date of recruitment	14 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 42
Country: Number of subjects enrolled	Spain: 8
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	13
From 65 to 84 years	33
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study population consisted of male and female subjects older than 50 years-old with Age-related Macular Degeneration (AMD) and naive Polypoidal Choroidal Vasculopathy (PCV).

Pre-assignment

Screening details:

Only treatment-naïve patients, 50 years of age or older, were recruited. Only eyes with a BCVA ETDRS letter score at study entry of 25 to 80 letters, and greatest linear dimension of the lesion of 5400 µm or less as assessed by fluorescein angiography and ICGA were included. 86 patients were screened, 36 of which failed the inclusion criteria.

Period 1

Period 1 title	Baseline - Week 0 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The Study Medication Aflibercept was open label, so unblinding was not applicable for Aflibercept. PDT was double-masked. The Investigator Sponsor and subject were not aware of the treatment being administered in case of PDT. The Monitor and Project Manager were unblinded. The double-blinding of the PDT was maintained throughout the conduction of the study. Only once all study data have been verified and the database locked, individual subjects were unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	IVA + Verteporfin PDT

Arm description:

Intravitreal Injection of Aflibercept 2 mg T&E + Verteporfin PDT

Arm type	Experimental
Investigational medicinal product name	AFLIBERCEPT+ VERTEPORFIN
Investigational medicinal product code	S01LA05 + S01LA01
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

40 mg/ml AFLIBERCEPT + 2 mg/ml verteporfin

Arm title	IVA + Sham PDT
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Arm description:

Intravitreal Injection of Aflibercept 2 mg T&E + Sham PDT

Arm type	Active comparator
Investigational medicinal product name	AFLIBERCEPT + SHAM
Investigational medicinal product code	S01LA05
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

40 mg/ml AFLIBERCEPT + 5% dextrose solution

Number of subjects in period 1	IVA + Verteporfin PDT	IVA + Sham PDT
Started	28	22
Completed	28	22

Baseline characteristics

Reporting groups

Reporting group title	Baseline - Week 0
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Reporting group description:

PCV cohort

Reporting group values	Baseline - Week 0	Total	
Number of subjects	50	50	
Age categorical			
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)	13	13	
From 65-84 years	33	33	
85 years and over	4	4	
Age continuous			
Units: years			
arithmetic mean	72.14		
standard deviation	± 9.17	-	
Gender categorical			
Units: Subjects			
Female	25	25	
Male	25	25	
Polyps			
Presence of polypoidal lesions			
Units: Subjects			
Presence	50	50	
BCVA			
Baseline BCVA			
Units: ETDRS letters			
median	66		
inter-quartile range (Q1-Q3)	56 to 70	-	

End points

End points reporting groups

Reporting group title	IVA + Verteporfin PDT
Reporting group description:	
Intravitreal Injection of Aflibercept 2 mg T&E + Verteporfin PDT	
Reporting group title	IVA + Sham PDT
Reporting group description:	
Intravitreal Injection of Aflibercept 2 mg T&E + Sham PDT	
Subject analysis set title	Study population
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients included were analysed.	

Primary: Change in BCVA

End point title	Change in BCVA
End point description:	
Change in BCVA from Baseline to week 52 (1-year)	
End point type	Primary
End point timeframe:	
From baseline to 1 year	

End point values	IVA + Verteporfin PDT	IVA + Sham PDT	Study population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	22	50	
Units: ETDRS letters				
median (inter-quartile range (Q1-Q3))	5 (2 to 13)	6.5 (2 to 11)	6 (2 to 12)	

Statistical analyses

Statistical analysis title	Change in BVCA
Statistical analysis description:	
Change in BCVA from Baseline to Week 52	
Comparison groups	IVA + Sham PDT v IVA + Verteporfin PDT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.98
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	90 %
sides	2-sided
lower limit	-1
upper limit	1

Notes:

[1] - Proof of concept analysis due to small sample size

Primary: Complete polyp occlusion

End point title	Complete polyp occlusion
End point description:	
End point type	Primary
End point timeframe:	
At week 52 (1 year).	

End point values	IVA + Verteporfin PDT	IVA + Sham PDT	Study population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	22	50	
Units: Number of subjects	17	17	34	

Statistical analyses

Statistical analysis title	Complete polyp occlusion
Statistical analysis description:	
Complete polyp occlusion at week 52	
Comparison groups	IVA + Verteporfin PDT v IVA + Sham PDT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.53 ^[3]
Method	Fisher exact
Parameter estimate	none
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1
upper limit	1

Notes:

[2] - Proof of concept analysis due to small sample size

[3] - Results for the primary objectives (i.e, change in BCVA from baseline to week 52, and polyp occlusion at week 52) were considered statistically significant if a test reached an α level of 0.025

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety results during the follow-up

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	IVA + Verteporfin PDT
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Reporting group description:

Intravitreal Injection of Aflibercept 2 mg T&E + Verteporfin PDT

Reporting group title	IVA + Sham PDT
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Reporting group description:

Intravitreal Injection of Aflibercept 2 mg T&E + Sham PDT

Serious adverse events	IVA + Verteporfin PDT	IVA + Sham PDT	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	1 / 22 (4.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Vulval cancer	Additional description: Vulvar skin cancer		
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker insertion	Additional description: Auricular fibrillation with pacemaker implantation		
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia	Additional description: Abdominal hernia		
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
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: 2 %

Non-serious adverse events	IVA + Verteporfin PDT	IVA + Sham PDT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 28 (57.14%)	9 / 22 (40.91%)	
Vascular disorders			
blood pressure high			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Vasculitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Systolic hypertension			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Hypertensive crisis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
retrosternal pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
allergic reaction to antibiotics			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Productive cough			

subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
expectoration subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Investigations intraocular pressure high subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	1 / 22 (4.55%) 2	
Injury, poisoning and procedural complications fractured metatarsal subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Stress fracture subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Procedural dizziness subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
finger traumatic amputation subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	Additional description: Palpitations 2 / 28 (7.14%) 2	0 / 22 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	0 / 22 (0.00%) 0	

facial neuralgia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
vasovagal reaction			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Inner ear disorder	Additional description: Vertigo		
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
wax in ear			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
deafness left ear			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Ocular hypertension			
subjects affected / exposed	1 / 28 (3.57%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
visual acuity decreased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	2 / 28 (7.14%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
Retinal pigment epithelial tear			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Posterior capsule opacification			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Blepharitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Keratitis			

subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
red eye subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
abdonimal pain subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Odynophagia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 0	0 / 22 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Renal and urinary disorders			
urinary incontinence aggravated subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
osteoarticular pain subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Groin pain subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
backache subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Infections and infestations			

Influenza subjects affected / exposed occurrences (all)	Additional description: Influenza viral infection		
	1 / 28 (3.57%) 1	2 / 22 (9.09%) 3	
Respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Respiratory tract infection - pathogen unspecified		
	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	Additional description: Urinary tract infection		
	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Herpes zoster subjects affected / exposed occurrences (all)	Additional description: Herpes viral infections		
	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Herpes ophthalmic subjects affected / exposed occurrences (all)	Additional description: Herpes ophthalmic Left Eye		
	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Conjunctivitis subjects affected / exposed occurrences (all)	Additional description: Conjunctivitis		
	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Otitis media subjects affected / exposed occurrences (all)	Additional description: Ear infection - otitis media		
	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Gastroenteritis subjects affected / exposed occurrences (all)	Additional description: Abdominal and gastrointestinal infections - pathogen unspecified		
	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Nasopharyngitis		
	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Metabolism and nutrition disorders			
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 22 (0.00%) 0	
Dyslipidaemia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 22 (4.55%) 1	
Hypercholesterolaemia			

subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2015	In Inclusion Criteria Number 5, 5400 mm was corrected to 5400 µm.
20 August 2015	Inclusion/exclusion criteria and rescue treatment criteria were updated
21 March 2018	Addition of a new procedure (blood collection for genetic analysis) and updating blinding and unblinding procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

low statistical power of the sample size and only one-year of follow-up

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34348351>