1 Synopsis

Sponsor-Investigator: Rufino Silva, MD, PhD- AIBILI	
Title of Study: 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)	
Investigators: Prof. Rufino Silva (Coordinating Investigator); Dr. Victor Àgoas/Dr. Sandra Barrão; Prof. Ângela Carneiro; Dr. Paulo Caldeira Rosa; Prof. João Figueira; Dr. Miguel Amaro; Dr. José Roque; Dr. Luís Mendonça; Prof. João Paulo Castro de Sousa; Dr. Angelina Meireles; Dr. Sara Vaz-Pereira; Dr. Sonia Viver; Dr. Laura Distefano; Dr. Alvaro Fernandez-Vega Sanz; Dr. Anniken Burés; Dr. Carlos Cava; Prof. Luis Arias Barquet; Prof. Francisco Cabrera Lopez	
Study centre(s): AIBILI – CEC- Centro de Ensaios Clínicos (CS001); Instituto de Oftalmologia Dr. Gama Pinto (CS028); Centro Hospitalar de São João (CS032); Instituto de Retina e Diabetes Ocular de Lisboa (CS080); Espaço Médico de Coimbra (CS082); Hospital Vila Franca de Xira (CS090); Instituto de Microcirurgia Ocular (CS102); Hospital Braga (CS103); Centro Hospitalar de Leiria (CS104); Hospital de Santo António (CD112); Hospital Santa Maria (CD117); Centro Oftalmologico Barraquer (CS026); Vall d'Hebron Hospital (CS074); Instituto Oftalmológico Fernandez-Vega (CS078); Instituto de Microcirugia Ocular (CS095); Complejo Hosp. Univ. Albacete (CS105); Bellvitge University Hospital (CD120); Hospital Insular de Gran Canaria (CD122)	
Publication (reference): Not applicable	
Studied period (years): 2016-2019 **First enrolment:** 25/02/2016 **Last completed:** 05/09/2018	**Phase of development:** Phase 4
Objectives: Primary objectives: 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. Secondary objectives: To evaluate the potential benefit, based on the secondary outcomes, of verteporfin PDT compared to sham PDT in AMD patients diagnosed with PCV treated with Aflibercept under a Treat and Extent treatment regimen. To evaluate the safety of Aflibercept treatment in patients with PCV. To characterize morphologically the 2 treatment regimens: Aflibercept T&E associated with verteporfin PDT and Aflibercept T&E associated with sham PDT. To identify potential genetic biomarkers of PCV. To identify genetic biomarkers of PCV that may influence treatment response; to identify genetic differences between PCV patients of Caucasian; and Asian populations - these results will be presented later in an addendum to this report.	
Methodology: This is a randomized, double-masked, sham-controlled, multi-centre pilot study to compare the efficacy and safety of intravitreal Aflibercept monotherapy with the efficacy and safety of combined treatment with Aflibercept associated with standard photodynamic therapy (PDT) with Verteporfin in age-related macular degeneration (AMD) patients with polypoidal choroidal vasculopathy (PCV) in a proof concept study and to identify genetic biomarkers for the diagnosis and treatment response of PCV in Caucasians.	
Number of patients (planned and analysed): The study population consists of male and female patients older than 50 years-old with Age-related Macular Degeneration (AMD) and Polypoidal Choroidal Vasculopathy (PCV). Planned: 50. Analysed: 50. (for genotyping 36 study samples and 49 control samples were analysed).	

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Either gender and Age ≥ 50.
2. Naïve PCV patients.
3. BCVA at study entry of 25 to 80 letters (Snellen Equivalent 20/320 to 20/25).
4. Diagnosis of symptomatic macular PCV in the study eye. Subfoveal involvement is required, with intraretinal or subretinal fluid and/or subfoveal PED, demonstrated on Spectral Dom–in - Optical Coherence Tomography (SD-OCT) (confirmed by the Central Reading Centre based OCT, Colour Fundus Photography (CFP), Fluorescein Angiography (FA) and Indocyanine Green Angiography (ICGA)).
5. Greatest linear dimension of the lesion of ≤ 5400 µm, assessed by FA/ICGA angiography.
6. Presence of PCV in the study eye assessed by the Central Reading Centre based on ICGA with active polyps with or without abnormal vascular network.
7. Women must be post-menopausal for at least 12 months prior to trial entry, or surgically sterile or in case of child-bearing potential, women must be using highly effective method of birth control (i.e. one that results in a failure rate less than 1% per year when used consistently and correctly, such as, combined hormonal contraception, progestogen-only hormonal contraception, intrauterine devices, intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, and sexual abstinence).
8. Ability to provide written informed consent.
9. Ability to return for all study visits.

Exclusion Criteria:

1. Active inflammation, infection or periocular infection in the study eye.
2. Uncontrolled intraocular pressure in the study eye.
3. Ocular condition in the study eye which may impact vision and confound study outcomes (e.g. vitreomacular traction, epirretinal membrane with BCVA impact, ocular inflammation, retinal vascular diseases like diabetic retinopathy or diabetic macular edema).
4. Presence of centromacular scarring or atrophy indicating irreversible BCVA loss.
5. Prior treatment of the study eye with anti-VEGF therapy.
6. Systemic use of anti-VEGF products within 3 months prior to the study entry.
7. Previous vitrectomy, aphakia, macular laser treatment, PDT, or intraocular steroids in the study eye.
8. Known serious allergies or history of hypersensitivity to fluorescein, indocyanine, verteporfin or components used of Eylea® formulation.
9. Subject with a condition (such as advanced, severe or unstable disease or its treatment) or is in a situation which may put him/her at significant risk, which may confound the study results or may interfere significantly with the subject's participation in the study.
10. History of porphyria and clinically relevant impairment of liver function.

Test product, dose and mode of administration, batch number:

This study included the following study medication:

• 40 mg/ml aflibercept (labelled Eylea®)

Eylea® 40mg/ml solution is formulated as a sterile solution for injection in a vial. Each vial contains 100 microliters, equivalent to 4 mg aflibercept, according to the Investigator Brochure.

Since marketed Eylea® was used, each box was labelled with the appropriate information stating that the medication was for use in this clinical trial only. Medication labels complied with the legal requirements and were printed in the local language. The storage conditions for study medication were described on the medication label.

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

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

Duration of treatment/follow-up: One year (12 months)

Criteria for evaluation: The study population consists of male and female patients older than 50 years-old with Age-related Macular Degeneration (AMD) and Polypoidal Choroidal Vasculopathy (PCV).

Efficacy: Efficacy has been assessed based on the following parameters: BCVA, SD-OCT and polyps' regression.

Safety: Safety parameters included assessment of intraocular pressure, adverse events (AE) and serious adverse events (SAEs).

Statistical methods:
Being a pilot study, no sample size was estimated**.**
Two analyses were performed for the primary objective considering the two primary outcomes, change in BCVA from Baseline to Week 52 and polyps' regression at Week 52.
A two-way factorial Analysis of Variance (ANOVA) with treatment group and need of PDT as fixed factors was used to assess the difference between treatments, Aflibercept associated with Verteporfin PDT and Aflibercept associated with Sham PDT, for the change in BCVA from baseline to Week 52.
For the polyps' regression at Week 52, a two-way factorial ANOVA with treatment group and need of PDT as fixed factors was also used to assess the difference between treatments, Aflibercept associated with Verteporfin PDT and Aflibercept associated with Sham PDT.
Statistically significant results for the primary objectives were considered if one of the tests reached a significant level of 0.025.
For the secondary objectives an exploratory analysis was performed, particularly for the evaluation of the potential benefit of more frequent Aflibercept treatment associated with PDT treatment in patients with suboptimal responses to T&E treatment regimen, in each study group.
For genotyping, GWAS genotyping of the study samples (plus control samples) was performed using the Illumina Human OmniExpress beadchips.

SUMMARY - CONCLUSIONS
Efficacy: Twenty-one patients (42%) had active polyps at week 16 and received PDT (sham or vPDT).
Regarding the primary outcome, change in BCVA from baseline to week 52, i.e., BCVA at week 52 minus BCVA at baseline, both groups had a 6 ETDRS letter gain at week 52 with a mean number of 7.96 ± 1.08 intravitreal aflibercept.
Concerning the primary outcome, polyps' regression at week 52, assessed by ICGA, a decrease in the mean area of polyps was seen in patients receiving Aflibercept + vPDT, although not statistically significant.
The primary efficacy analysis with the FAS and PP population yields similar results. Thus, the analysis on the FAS was considered as main to avoid any bias.
For the secondary outcomes, a decrease in the mean CRT from baseline was verified in both treatment groups, no meaningful differences were detected in macular fluid or in the number of intravitreal aflibercept. Number of active/sham PDT treatments presented similar proportions from both groups qualified for active or sham PDT.
Although no statistically significant differences between groups were found at each study visit, BCVA change over time was statistically significant (p=0.034) considering the interactions between the need of PDT and the treatment group. The mean change in BCVA from baseline to week 16 is similar in both groups, and only the need of PDT was significantly different between groups (p=0.016). No significantly different between groups (p=0.320) were found in BCVA gain, loss or maintenance at week 52.
The polyps' regression at week 16 and week 52 did not differ significantly between groups.
Using GWAS-array data from GAMA consortium consisting of 1062 PCV, 1157 typical AMD (tAMD) and 5275 shared controls, we found that common SNPs underlying PCV and typical AMD were substantially overlapped (rg = 0.69; P = 4.68 x 10-3)1. ARMS2-HTRA1 (rs10490924; A69S) and CFH (rs800292 ; I62V) were confirmed to be the loci most strongly associated with PCV.

Overall conclusions: This is the first randomized clinical trial in Caucasian patients with PCV comparing T&E IVA monotherapy versus T&E IVA + vPDT.
Both groups had a 6 ETDRS letter gain at week 52 with a mean number of 7.96 ± 1.08 intravitreal aflibercept.
After the loading phase of IVA, only 42% of the eyes qualified PDT for active/sham PDT.
Verteporfin PDT was performed in 22% of the eyes (mean number of verteporfin PDT treatments 1.00 ± 0.0) and showed no additional benefit in the BCVA results or polyp regression at week 52.
For the secondary outcomes, a decrease in the mean central retinal thickness from baseline was verified in both treatment groups and no meaningful differences were detected in macular fluid or in the number of intravitreal aflibercept. Number of active/sham PDT treatments presented similar proportions from both groups qualified for active or sham PDT.
No new or additional adverse events beyond those previously observed in trials of IVA or other anti-VEGF agents were found.
ARMS2-HTRA1 (rs10490924; A69S) and CFH (rs800292 ; I62V) were confirmed to be the loci most strongly associated with PCV.

Date of the report: 12/12/2019