

BMJ Open Protocol for a randomised, double-masked, sham-controlled phase 4 study on the efficacy, safety and tolerability of intravitreal aflibercept monotherapy compared with aflibercept with adjunctive photodynamic therapy in polypoidal choroidal vasculopathy: the ATLANTIC study

João Pedro Marques,^{1,2,3} Cláudia Farinha,^{1,3} Miguel Ângelo Costa,¹ Ângela Ferrão,¹ Sandrina Nunes,¹ Rufino Silva^{1,3,2}

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For numbered affiliations see end of article.

Correspondence to

Dr João Pedro Marques;
marquesjoapetro@gmail.com

ABSTRACT

Purpose The purpose of this study is to compare the efficacy and safety of intravitreal aflibercept (IVA) with sham photodynamic therapy (sPDT) versus IVA with verteporfin PDT (vPDT) in a Caucasian population with treatment-naïve polypoidal choroidal vasculopathy (PCV), enrolling into a treat and extend (T&E) regimen.

Methods and analysis Randomised, double-masked, sham-controlled, multicentre phase 4 investigator-driven clinical trial. The primary outcomes are (1) change in best-corrected visual acuity (BCVA) from baseline and (2) polyp regression at week 52, assessed by indocyanine green angiography (ICGA). Fifty patients with treatment-naïve PCV will be recruited from Portuguese and Spanish clinical sites. Eligible patients will receive monthly IVA for 3 months (week 0, week 4 and week 8). At week 16, all patients will repeat ICGA and undergo central randomisation (1:1 ratio) into one of the following groups: Group 1—IVA T&E + vPDT; Group 2—IVA T&E + sPDT. PDT will be performed at week 16, week 28 and week 40 in the presence of active polyps. After week 16, the presence of macular fluid on optical coherence tomography will determine the schedule of observations. When present, the interval between visits/injections will decrease 2 weeks (minimum 6 weeks). When not, the interval between visits/injections will increase 2 weeks (maximum 12 weeks). Efficacy will be evaluated based on BCVA, central retinal thickness and polyp regression. Safety parameters will include assessment of intraocular pressure, adverse events and serious adverse events.

Ethics and dissemination This study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. The

Strengths and limitations of this study

- First randomised clinical trial in a Caucasian population conducted to evaluate the safety and efficacy of aflibercept in polypoidal choroidal vasculopathy, either alone or in combination with photodynamic therapy.
- Multicentre, double-masked, sham-controlled clinical trial.
- Since it is mainly a proof of concept study with a relatively small study population, further validation of its main results will be needed.

study received approval from Comissão de Ética para a Investigação Clínica and Comité Ético de investigación Clínica del Hospital Universitari de Bellvitge.

Trial registration number This study is registered under the EudraCT number: 2015-001368-20 and the ClinicalTrials.gov Identifier: NCT02495181.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is an increasingly recognised neovascular phenotype of age-related macular degeneration (AMD), representing up to 13% of choroidal neovascularisation (CNV) cases in Caucasians and up to 50% in Asians.^{1,2} While PCV and typical exudative AMD share some clinical features and risk factors, differences regarding the genetic background, epidemiological characteristics, natural history and treatment outcomes point to distinct pathophysiological processes.^{1,3,4} The intravitreal

injection of anti-vascular endothelial growth factor (anti-VEGF) is now the mainstay of treatment of wet AMD. However, the use of anti-VEGF compounds in monotherapy in PCV has been associated with a lower rate of polyp closure, despite the good visual outcomes. In the EVEREST study,⁵ a 6-month multicentre, randomised clinical trial (RCT) conducted to evaluate the efficacy and safety of verteporfin photodynamic therapy (vPDT) with or without 0.5 mg ranibizumab versus ranibizumab 0.5 mg monotherapy in Asian patients with symptomatic PCV, the authors reported a significantly lower rate of complete polyp regression in the ranibizumab monotherapy group (28.6%) than in the PDT-containing treatment arms (77.8% in the PDT plus ranibizumab arm and 71.4% in the PDT monotherapy arm). All treatment arms showed an improvement of best-corrected visual acuity (BCVA) from baseline, with patients in the combination group achieving the highest gain (+10.9 letters from baseline). The proportion of patients gaining ≥ 15 letters was 21% in the vPDT + ranibizumab group, 19% in the vPDT group and 33.3% in the ranibizumab monotherapy group. However, BCVA differences between groups were not statistically significant. Another study in an Asian population, the LAPTOP study,^{6,7} randomised patients with PCV to either ranibizumab monotherapy or PDT monotherapy. A higher proportion of patients in the ranibizumab arm gained 0.2 logMAR than those in the PDT arm, both at 12 and 24 months. Nevertheless, the polyp regression rate was not evaluated. In 2013, a group of experts published a set of guidelines for the management of PCV⁸ and recommended a combination of indocyanine green angiography (ICGA) guided PDT with Verteporfin and 3 monthly injections of ranibizumab 0.5 mg as the initial treatment of active juxtafoveal and subfoveal PCV. A systematic review and meta-analysis published by Wang *et al*⁹ concluded that even though combined treatment (PDT + ranibizumab 0.5 mg) appeared to result in better visual acuity and lower retinal haemorrhage, it did not affect the resolution and recurrence of lesions.

Given the introduction of aflibercept in clinical practice and its promising results in typical exudative AMD,¹⁰ clarifying its anatomical and functional outcomes in the treatment of PCV, either alone or in combination with PDT, is an unmet medical need. Previously known as VEGF trap-eye,¹¹ aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, New York, USA) is a chimeric molecule composed of an Fc fragment linked to the extracellular portions of the VEGFR1 and VEGFR2 receptors. It binds to all isoforms of VEGF, thus preventing activation of VEGF receptors.¹² The approved treatment regimen for wet AMD is one injection per month for three consecutive months, followed by one injection every 2 months (2 mg every 8 weeks—2Q8). Kikushima *et al*¹³ retrospectively evaluated the results of aflibercept monotherapy versus a combined regimen of aflibercept and PDT in an Asian population with PCV. The authors reported that the combined treatment might be superior to aflibercept monotherapy in terms of disease-stabilising efficacy, but with an equivalent

visual gain at 12 months.¹³ However, to the best of our knowledge, no RCT has been conducted in Caucasians to evaluate the safety and efficacy of aflibercept in PCV, either alone or in combination with PDT. Considering that several genetic variants associated with PCV do not seem to translate across ethnic lines,^{3,14–16} it is important as a proof of concept to evaluate if a combination regimen is superior to anti-VEGF monotherapy in the specific setting of a Caucasian population. There is also some controversy regarding the real need of closing all the polyps when treating PCV. In fact, based on the visual acuity results of the EVEREST study,⁵ many ophthalmologists are currently treating PCV with anti-VEGF monotherapy. A treat and extend (T&E) regimen using aflibercept with or without PDT may answer these questions, eventually leading to a paradigm shift in the current management of PCV. The importance of this study lies in the possibility of providing responses to the following questions: (1) is aflibercept safe when used in combination with PDT? (2) can combination therapy of aflibercept plus PDT improve the anatomical and functional results in PCV when compared with aflibercept monotherapy? (3) is the currently approved aflibercept treatment regimen for typical exudative AMD effective in PCV? (4) what is the best injection interval for aflibercept in PCV eyes?

The primary objective of this study is to compare the efficacy and safety of intravitreal aflibercept (IVA) with sham PDT (sPDT) versus IVA with vPDT in a Caucasian population with treatment-naïve PCV, undergoing a T&E regimen.

METHODS AND ANALYSIS

Study type and study design

Randomised, double-masked, sham-controlled, multicentre phase 4 investigator-driven clinical trial registered under the EudraCT number: 2015-001368-20 and the ClinicalTrials.gov Identifier: NCT02495181 (see online supplementary file 1).

Study title

A randomised, double-masked, sham-controlled phase 4 study of the efficacy, safety and tolerability of intravitreal aflibercept monotherapy compared with aflibercept with adjunctive photodynamic therapy in patients with polypoidal choroidal vasculopathy

Study acronym

ATLANTIC

Sponsor

AIBILI—Association for Innovation and Biomedical Research on Light and Image

Contact name: Sandrina Nunes

Address: Azinhaga de Santa Comba, Celas, 3000–548 Coimbra, Portugal

Tel: +351 289 480 137

Email: 4c@aibili.pt

Principal investigator

Rufino Silva MD, PhD

Central Reading Centre

Coimbra Ophthalmology Reading Centre (CORC)

EVICR.net Coordinating Centre

AIBILI–EVICR.net Coordinating Centre

Study outcomes*Primary outcomes*

The primary outcomes of the study are:

1. Change in BCVA from baseline to week 52
2. Polyp regression at week 52, assessed by ICGA

Secondary outcomes

The secondary outcomes of the study are:

1. Change in BCVA over time
2. Change in BCVA at week 16
3. BCVA gain ≥ 5 , 10 or 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters at week 52
4. BCVA loss ≥ 5 , 10, 15 or 30 ETDRS letters at week 52
5. BCVA stabilisation at week 52 (BCVA change from baseline between -5 and $+5$ ETDRS letters, exclusively)
6. Polyp regression at week 16, assessed by ICGA
7. Complete polyp regression at week 52, assessed by ICGA
8. Complete polyp regression at week 16, assessed by ICGA
9. Presence of active polyps at week 52, assessed by ICGA
10. Presence of active polyps at week 16, assessed by ICGA
11. Presence of leakage on fluorescein angiography (FA) at week 52
12. Change in the central retinal thickness (CRT) over time (assessed by spectral domain optical coherence tomography (SD-OCT))
13. Presence of macular fluid at week 52 (assessed by SD-OCT)
14. Total number of intravitreal injections of aflibercept
15. Total number of treatments with vPDT
16. Frequency and severity of ocular and non-ocular adverse events (AEs) over time

Outcome definitions

- ▶ BCVA will be determined according to the ETDRS protocol in all visits
- ▶ Polyp regression will be defined as a reduction in the total area of polyps, quantitatively assessed by certified graders of the Central Reading Centre
- ▶ Complete polyp regression will be defined as polyp inactivity/disappearance, assessed by ICGA
- ▶ Polyp activity will be defined as the presence of single or multiple (cluster or string) hyperfluorescent round/oval lesions on ICGA, within the first 6 min after injection, with one or more of the following characteristics
 - Nodular appearance on stereoscopic view of ICGA

- Hypofluorescent halo surrounding the focal hyperfluorescent lesion(s) on early frames
 - Pulsatile filling of the lesion
 - Leakage in the late frames
- ▶ Polyp inactivity (of the polyps that remain visible) will be defined by an hypofluorescent lesion core in the ICGA late phases (washout of the dye), producing a ring-like staining of the polypoidal lesion(s) but without associated leakage

Efficacy assessment

Efficacy will be assessed based on the following parameters: BCVA, SD-OCT parameters (including the presence of intraretinal or subretinal fluid, the CRT variation and so on) and polyp regression (evaluated by ICGA).

Safety assessment

Safety parameters will include assessment of intraocular pressure (IOP), AEs and serious adverse events (SAEs).

Timelines

- ▶ Competitive recruitment started in November 2015
- ▶ Patient follow-up: 1 year after inclusion

Sample selection

The study population will consist of male and female subjects older than 50 years with treatment-naive PCV. Each investigator will recruit patients from his/her clinical practice, from approximately 20 clinical sites in Portugal and Spain. A total number of 50 subjects are expected to be enrolled in the study.

Eligibility criteria

Both eyes will be assessed at the screening visit for eligibility and only one eye will be selected from each subject as the study eye. Subjects who sign the informed consent form will participate in a screening period (maximum 21 days) to confirm eligibility by the Central Reading Centre—CORC. In case both eyes meet the eligibility criteria, the study eye will be the one with the worst BCVA.

Inclusion criteria

1. Age ≥ 50 .
2. Either gender.
3. Patients with Treatment-naive PCV.
4. BCVA at study entry from 25 to 80 ETDRS letters (Snellen Equivalent 20/320 to 20/25)
5. Presence of PCV in the study eye assessed by the Central Reading Centre based on multimodal retinal imaging (colour fundus photography (CFP), SD-OCT, FA and ICGA), including the presence of active polyps on ICGA, with or without branching vascular network (BVN). Subfoveal involvement is required, with intraretinal or subretinal fluid and/or subfoveal pigment epithelium detachment (PED) seen on SD-OCT.
6. Greatest linear dimension (GLD) of the lesion on FA and ICGA ≤ 5400 μm . Using the Heidelberg software,

the total lesion is outlined manually, encompassing the BVN as well as all the polyps and any type 2 CNV component. The best-fit circle is then manually drawn around the total lesion outline. The circle's diameter is used as the GLD of the lesion.

7. Women must be postmenopausal for at least 12 months prior to trial entry, or surgically sterile, or in case of childbearing potential, women must be using highly effective method of birth control (ie, 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, bilateral tubal occlusion, vasectomised partner and sexual abstinence).
8. Ability to provide written informed consent.
9. Ability to return for all study visits.

Exclusion criteria

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

Patient withdrawal

Study medication must be discontinued and the subject withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that subject. The following circumstances require study discontinuation:

- ▶ Loss ≥ 15 ETDRS letters of BCVA from baseline.
- ▶ Withdrawal of informed consent.
- ▶ Any other protocol deviation that results in a significant risk to the subject's safety.

Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits or become lost to follow-up for any other reason. If a subject chooses to stop study treatment, the investigator should encourage the subject to return for a last visit.

Before discontinuation, the subject should attend a visit with the same procedures as in the discharge visit. If premature withdrawal occurs for any reason, the investigator must make all attempts to determine the primary reason for a subject's premature withdrawal from the study and record this information on the study discharge case report form (CRF) page.

Study assessments and visit schedule

Study procedures/data acquisition

Ophthalmological examination

A standard slit-lamp ophthalmological examination will be performed in all visits in both eyes. The fundus will be observed after pupil dilation with eye drops. IOP will be measured prior to pupil dilation and always using the same type of equipment throughout the clinical trial. IOP will also be measured before and after the aflibercept injection. After the screening visit, the electronic CRF (eCRF) will only include data from the study eye.

Best-corrected visual acuity (BCVA)

BCVA will be evaluated in both eyes according to the ETDRS protocol in all visits.

Spectral domain optical coherence tomography (SD-OCT)

SD-OCT (macular acquisitions) will be performed in both eyes after pupil dilation, according to [table 1](#) and must be sent to the Central Reading Centre for analysis. The study allows the use of Heidelberg Eye Explorer Spectralis SD-OCT, Cirrus HD OCT, Topcon 1000/2000/Swept Source OCT Viewer and NAVIS-EX Nidek SD-OCT. The scanning protocol involves a macular cube acquisition, radial acquisition and linear acquisition. Operator and equipment certification is required before starting to acquire OCT examinations under the study protocol. The Central Reading Centre will provide a specific protocol detailing acquisition, export and submission procedures as well as instructions for prior certification activities.

Colour fundus photography (CFP), fluorescein angiography (FA) and indocyanine green angiography (ICGA)

Digital CFP, FA and ICGA of fields 1 and 2 at 30°/35° will be performed on both eyes after pupil dilation according to [table 1](#) and must be sent to the Central Reading Centre for analysis.

ICGA will be performed at baseline, week 16 and week 52 in all subjects. ICGA may be repeated at weeks 28 and 40 if (1) there is a decline ≥ 5 letters on BCVA comparing to the highest BCVA during the study period and (2) there is evidence of macular fluid on SD-OCT. Photographer and equipment certification is required before

Table 1 Study assessments and visit schedule during the different study phases

Study phase	Screen phase		Loading phase		Treat and extend phase																Primary Endpoint
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18			
Cumulative visit number*	-21 to 0	Week 0	Week 4	Week 8	Week 16	Week 22	Week 26	Week 28	Week 28	Week 34	Week 36	Week 38	Week 40	Week 42	Week 44	Week 46	Week 48	Week 50	Week 52		
Procedure																					
Informed consent	X																				
Inclusion/exclusion	X																				
Demographics	X																				
Medical/ocular history	X																				
Physical examination	X																				
Vital signs (blood pressure and pulse rate)	X				X							X								X	
Urine pregnancy test†	X																				
Fundus examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Slit lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SD-OCT	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	X [§]	
CFP	X [§]				X [§]			(X [§])				(X [§])								X [§]	
FA	X [§]				X [§]			(X [§])				(X [§])								X [§]	
ICGA	X [§]				X [§]			(X [§])				(X [§])								X [§]	
IVA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PDT					(X)			(X)				(X)									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study discharge																				X	

*PDT will be allowed at weeks 16, 28 and 40, if needed.
 †Allowed Window (±5 working days).
 ‡For women of childbearing potential.
 §Images to be sent to the Central Reading Centre (the reading centre will confirm patients eligibility).
 Bsl, baseline; BCVA, best-corrected visual acuity; CFP, colour fundus photography; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; ICGA, indocyanine green angiography; IOP, intraocular pressure; IVA, intravitreal aflibercept; PDT, photodynamic therapy; SD-OCT, spectral domain optical coherence tomography.

starting to acquire images under the study. The Central Reading Centre will provide a specific protocol detailing acquisition, export and submission procedures as well as instructions for prior certification activities.

Patient identification

Each subject will be uniquely identified by a subject identification code. This code is only used for study purposes. On signing the informed consent form, the subject will be identified by this subject identification code. This code will consist of a combination of three fixed digits '209', plus three digits for the site number and two sequential digits for the subject number. For example, the first patient included in clinical sites number 001 and 015 will be 20900101 and 20901501, respectively. Once assigned to a subject, the subject identification code will not be reused.

Blinding/unblinding procedures and randomisation

The study medication (aflibercept) will be open label. Unblinding will not be applicable for aflibercept. The use of PDT will be double-masked. The investigator,

sponsor, subject and monitor involved in reporting, obtaining and/or reviewing the clinical evaluations will not be aware of the treatment being administered in case of PDT. The double-blinding of the PDT will be maintained throughout the study. Only once all study data have been verified and the database locked, individual subjects will be unblinded. In the event that an emergency blind break is required, the treatment that the subject has received will be provided to the investigator. In case a suspected unexpected serious adverse reaction (SUSAR) occurs during the study, the sponsor's pharmacovigilance department (or designee) will be able to break the blind in order to comply with legal expedited reporting requirements.

The randomisation will be centrally generated and assigned to eligible subjects/eyes in order to balance the subject allocation between treatment arms. This will take place at week 16, where all patients will be randomised in a 1:1 ratio into one of the following groups:

- Group 1: Intravitreal injection of aflibercept 2 mg/0.05 mL T&E + vPDT

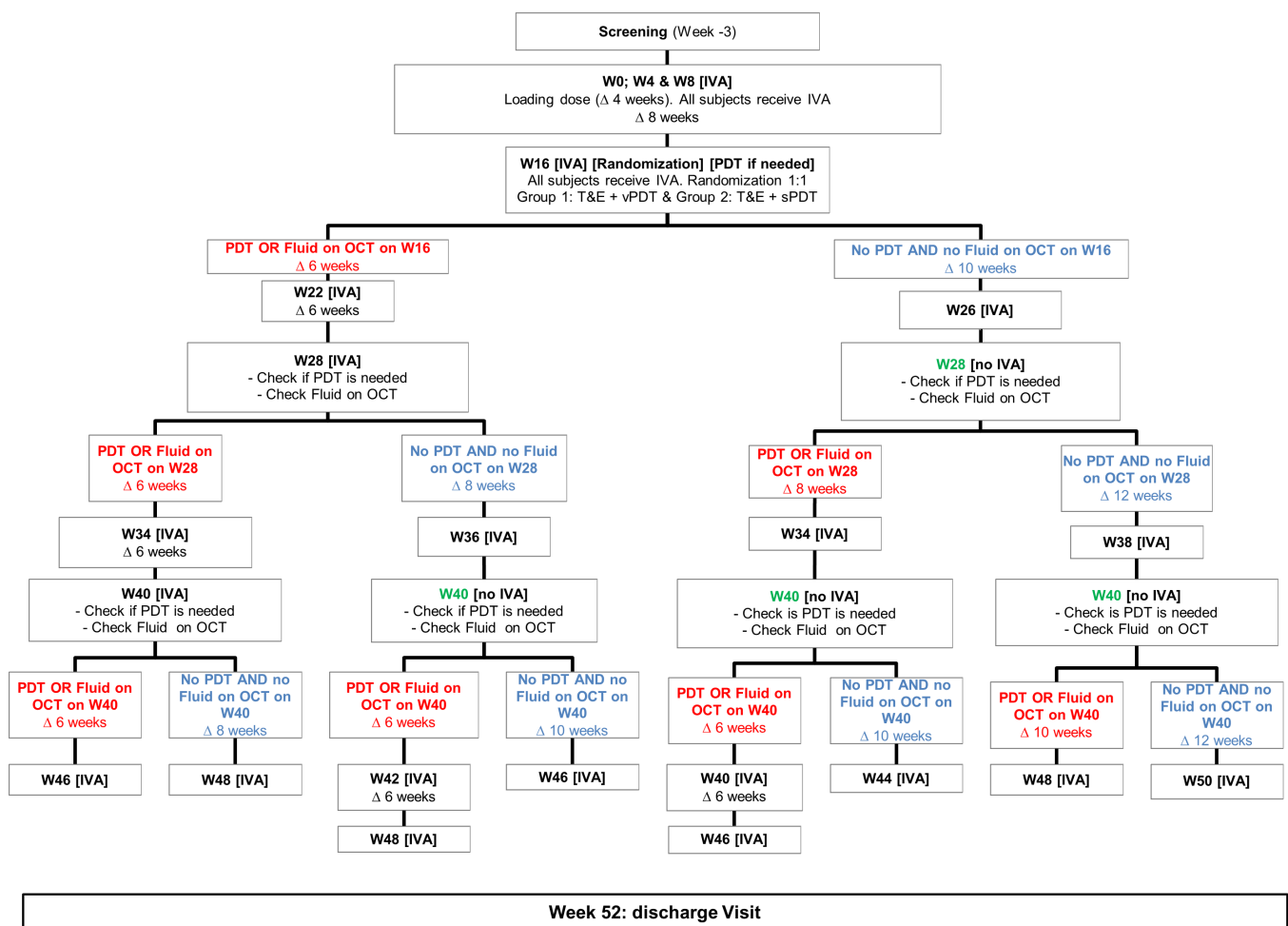


Figure 1 Diagram flow of the study. IVA, intravitreal aflibercept; OCT, optical coherence tomography; PDT, photodynamic therapy; vPDT, verteporfin photodynamic therapy; sPDT, sham photodynamic therapy; T&E, treat and extend.

- ▶ Group 2: Intravitreal injection of aflibercept 2 mg/0.05 mL T&E + sPDT

ICGA is mandatory at week 16 and will be the basis to differentiate patients with active and patients with inactive polyps. Every subject will receive an intravitreal injection of aflibercept, despite the treatment group or the polyp activity. However, PDT (vPDT and sPDT) will only be applied in the presence of active polyps confirmed by ICGA. This means that both groups will include patients who will and patients who will not undergo PDT at week 16 (figure 1).

Screening failures

Subjects discontinuing prior to the first injection of aflibercept are considered screening failures. All data collected during the screening visit will be registered as well as the reason for not starting treatment.

Study completion

Subjects who successfully complete the study through week 52 will be considered to have completed the study for data analysis.

Early study termination

The study can be terminated at any time by the sponsor, the competent authorities (CAs) or by the Institutional Review Board/Independent Ethics Committees (IRB/IEC). Should this be necessary, subjects should be seen as soon as possible and treated as described for a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the subjects' interests.

Treatment

Investigational and control treatment

Treatment arms

If a subject's eligibility is confirmed, the patient will receive one intravitreal injection of aflibercept 2 mg/0.05 mL per month for three consecutive months (weeks 0, 4 and 8)—loading phase (figure 1).

Subjects will return for treatment at week 16. At this point, they will be randomised in a 1:1 ratio into one of the following groups:

- ▶ Group 1: Intravitreal injection of aflibercept 2 mg/0.05 mL T&E + vPDT
- ▶ Group 2: Intravitreal injection of aflibercept 2 mg/0.05 mL T&E + sPDT

Note:

- ▶ At week 16, all subjects receive IVA.
- ▶ PDT (vPDT or sPDT) will only be used in the presence of active polyps on ICGA. Treatment will be performed with ICGA-guided standard fluence vPDT, as described by the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) study group¹⁷ (verteporfin dose of 6 mg/m² of body surface; light dose of 50 J/cm²; exposure time of 83 s). The irradiated area will depend on the lesion's GLD

measured on ICGA, plus an extra 500 µm margin on each side (1 mm extra).

- ▶ The need for further PDT will again be assessed by ICGA on weeks 28 and 40 if (1) there is a decline ≥ 5 letters on BCVA comparing to the highest BCVA during the study period and 2) there is evidence of macular fluid on SD-OCT. If ICGA confirms the presence of active polyps, PDT will be used, within 1 week after the intravitreal injection of aflibercept.
- ▶ After week 16, the frequency of injections will depend on the presence of macular fluid (6 mm central) assessed by SD-OCT. When macular fluid is confirmed by SD-OCT, the interval between injections will decrease 2 weeks, up to a minimum of 6 weeks. On the other hand, if macular fluid is not present on SD-OCT, the interval between visits will increase 2 weeks, up to a maximum of 12 weeks.
- ▶ Since the frequency of study visits will depend on the presence of macular fluid on SD-OCT at weeks 16, 28 and 40, the number of visits per patient will range from 11 to 12 visits.

Patient treatment assignment

At week 0, subjects who fulfil all the eligibility criteria will start treatment with aflibercept (weeks 0, 4 and 8). At week 16, subjects will be given a randomisation number. This number assigns them to one of the treatment arms (vPDT or sPDT). The randomisation numbers will be centrally generated in order to ensure that treatment assignment is unbiased. A randomisation list will be produced by the coordinating centre using a validated system that randomly assigns treatment arms to randomisation numbers in the specified ratio 1:1 and according to stratification by polyp activity (indicated by ICGA). In case of dropout, previously randomised subjects will not be replaced.

Study treatment

Study medication

This study will include the following study medication:

- ▶ 40 mg/mL aflibercept (labelled Eylea)

Dosage form, packaging and labelling

Eylea 40 mg/mL solution is formulated as a sterile solution for injection in a phial. Each phial contains 100 µL, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 µL containing 2 mg aflibercept. Aflibercept must be stored according to the label instructions contained on the summary of the product characteristics (SmPC) and it must be kept in a secure locked facility. Since marketed Eylea will be used, each box will be labelled with the appropriate information stating that the medication is for use in this clinical trial only. Medication labels will comply with the legal requirements and be printed in the local language. The storage conditions for study medication will be described on the medication label.

Dispensing

Study medication will be dispensed to the subjects according to this protocol and with the given instructions.

Storage and drug accountability

The study medication will be stored in accordance with ICH-good clinical practice (GCP) and SmPC. The study medication should be received by the principal investigator or designee at the clinical site, handled and stored safely and properly and kept in a secure location to which only the principal investigator and designated assistants have access.

In the clinical sites, a temperature log will be maintained, documenting appropriate medication storage conditions and will be made available for the monitor to inspect.

During the study, the principal investigator or designee will conduct an inventory of the study medication and maintain records of the study medication dispensing for each subject. This record will be made available to the monitor for the purpose of verifying the accounting of medication. Any discrepancies and/or deficiencies between the observed disposition and the written account will be recorded along with an explanation. The principal investigator will also ensure that the study medication will not be used in any unauthorised manner.

Photodynamic therapy (PDT)

- ▶ 2 mg/mL verteporfin (labelled Visudyne)
- ▶ 5% dextrose solution (sPDT)

Verteporfin will be used for the vPDT while the 5% dextrose solution will be used for the sPDT. Each clinical site will purchase verteporfin to perform PDT to its subjects, according to the current package labelling and SmPC.

Masking

PDT will be double-masked; therefore, each member of the investigational team must remain either masked or unmasked to the treatment assigned for each subject along the conduction of the study in order to avoid bias (table 2).

Masked roles

The masked investigational team will perform all procedures, except the treatment with PDT and the accountability/handling of PDT medication. An

independent monitor will be responsible for pharmacy site visits and will be unmasked to treatment. Further, the subjects will also remain masked along the conduction.

Under no circumstances the unmasked study pharmacist and/or study nurse will perform efficacy and safety procedures.

Unmasked roles

Only the pharmacist and/or the study nurse who performs the drug accountability and/or prepares the PDT treatment will be unmasked. They will not have any other role in the study. The verteporfin infusion and the sham infusion will be covered by foil paper or other material so that the investigator is not aware if the treatment is vPDT or sPDT. Independent study personnel responsible for drug supply and unmasked monitors who are not involved in the conduction of the study can also be unmasked.

Instructions for prescribing and performing/taking the study treatments

After the mandatory loading phase in weeks 0, 4 and 8, the frequency of the injections will depend on the presence/absence of macular fluid (6 mm central) assessed by SD-OCT at weeks 16, 28 and 40.

Permitted study treatments adjustments and interruptions

Study medication dose adjustments are not permitted.

Treatment exposure and compliance

The investigator should promote compliance by informing the subject of the importance of attending each scheduled visit in order to monitor the subject's safety, efficacy and the validity of the study. The subject should be instructed to contact the investigator if he/she is unable to attend the study visits.

Rescue treatments

If a subject needs a rescue treatment different from the study treatments due to severe vision loss (15 or more letters of BCVA compared with baseline) or safety reasons, he/she must be withdrawn from the study before treatment is performed.

Concomitant treatment

Any concomitant medication used by a subject from the date of enrolment (screening visit) until the conclusion of the study participation (except for routine medications given for ocular procedures required by the protocol, ie, fluorescein, indocyanine, dilating drops, topical antibiotic, topical anaesthetic) should be recorded on the concomitant medication CRF page including start and stop dates and indication.

The following treatments are not allowed during the study:

- ▶ Anti-VEGF therapy (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab and so on) or intravitreal corticosteroids in the study eye.
- ▶ Systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chlo-

Masked/unmasked	Investigational team
Masked	Principal investigator
	Investigator
	Study coordinator
	Technicians
Unmasked	Study nurse
	Pharmacist

roquine/hydroxychloroquine (plaquenil), tamoxifen, phenothiazines and ethambutol.

If the fellow-eye needs treatment for wet AMD (including PCV), subjects can be treated with any medication according to clinical practice and continue in the study.

The investigator should instruct the subject to notify the investigator about any new medications he/she takes after the start of the study. All medications (other than study medication and routine medications given for ocular procedures required by the protocol) and significant non-drug therapies must be recorded on the concomitant medication CRF page.

Emergency unblinding

In case of a SUSAR, the treatment code (PDT versus SPDT) will usually be unblinded. In case of other medical emergency or other situation in which the knowledge of a subject's assigned treatment is essential to medical management of the subject, the investigator may unmask the treatment group of the subject.

Each unblinding has to be reported to the sponsor and also the reason for unblinding. Preferably, the investigator should inform the sponsor before the unblinding.

Unblinding will lead to the disqualification of the subject for the statistical analysis.

Study completion and poststudy treatment

The end of the study corresponds to the last visit of the last subject in the last clinical site. Subjects completing the study will be treated at hospital or private clinic according to accepted medical practice. The investigator should also provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

Efficacy assessments

Parameters

Efficacy will be assessed based on the following parameters: BCVA, SD-OCT and polyp regression.

Monitoring

Efficacy monitoring will be assessed through the efficacy parameters progression from baseline to week 52.

A data management plan and monitoring plan (MP) will be elaborated.

Safety assessments

Parameters

Safety parameters will include assessment of IOP, AEs (see Section 'Adverse events') and SAEs (see Section 'Serious adverse event reporting and follow-up').

Monitoring

Safety assessment will consist of measuring IOP and monitoring/recording all safety parameters from baseline to week 52. A MP of the clinical trial will be elaborated to list in detail how safety monitoring will be conducted.

Adverse events

An AE is any unfavourable and unintended sign (eg, including an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational medicinal product and/or any study procedure, whether or not considered related to the investigational medicinal product.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. AEs may also be detected when they are voluntarily reported by the subject during or between visits or through physical examination, laboratory testing, or other assessments. All AEs must be recorded on the adverse event log of the CRF. All AEs will be collected from the first day until 30 days after discontinuation/completion of study participation even if the event is not considered to be related to the study medication.

Medical conditions/diseases present before starting the study are only considered AEs if they worsen after starting the study (exacerbation). Abnormal laboratory values or test results constitute AEs only if the investigator considers them clinically significant and requiring treatment adjustment, transitory or permanent study medication discontinuation or any other interventional measure or diagnostic evaluation of subject risk. They should be investigated and monitored appropriately.

Serious adverse events

Definitions

Serious adverse event (SAE) and serious adverse reaction (SAR)

Any untoward medical occurrence or effect that, at any dose:

- ▶ results in death,
- ▶ is life threatening,
- ▶ requires hospitalisation or prolongation of existing hospitalisation,
- ▶ results in persistent or significant disability or incapacity,
- ▶ is a congenital anomaly or birth defect,
- ▶ is an important medical event.

Serious unexpected suspected adverse reaction (SUSAR)

Any SAR with a nature or severity that is not described in the Reference Safety Information (ie, the SmPC for an authorised product).

The following AE do not need to be managed as serious:

- ▶ Hospitalisation for routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- ▶ Hospitalisation for elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study.
- ▶ Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.

The other SAEs should be reported as specified below.

Reporting and follow-up

In case of a SAE, the investigator has to immediately report to the sponsor or designee all SAEs with the exception of those that are identified as not requiring immediate reporting in the protocol.

If a SAE occurs, the investigator must fill in a SAE form within 24 hours of learning of its occurrence. This is also applicable to any SAE that occurs within 30 days after study medication discontinuation.

The sponsor or designee is responsible for submitting to CAs and Ethic Committees all SUSARs collected during the study, following the procedure and time frame described in the legislation currently in force.

The sponsor or designee will also report, in an expedited manner, any other safety information that could modify the benefit-risk balance of the investigational drug.

Pregnancy

Women of childbearing potential who are not using adequate birth control will be excluded from the study. Nevertheless, any pregnancy that occurs during the study, although not itself an SAE, should be recorded and reported by the investigator to the sponsor within 24 hours of learning of its occurrence to facilitate outcome follow-up.

Abortion, whether it is accidental, therapeutic or spontaneous, should be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the investigational treatment should be reported as an SAE.

Female subjects must be instructed to stop taking the study medication and immediately inform the investigator if becoming pregnant during the study. Pregnancies beginning within 30 days after the completion of the last dose of study medication must also be reported to the investigator. The investigator should counsel the subject, discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a subject participating in the study should also be reported to the investigator and sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study medication of any pregnancy outcome.

Annual safety report

Annually, the sponsor or designee will prepare a Development Safety Update Report (DSUR) that will include all SAEs and SUSARs collected during the reporting period. The sponsor will submit the DSUR to CAs and involved Ethic Committees, following the time frame established in the legislation currently in force.

Data analysis

Sample size

Fifty patients, approximately 25 from each country (Portugal and Spain), will be considered for this study. Since it is a pilot study, no sample size estimation was performed.

Population(s) for analysis

The intent-to-treat (ITT) and per-protocol (PP) populations will be considered for analysis. The ITT population will be used for the primary efficacy analysis. In a second analysis, the PP population will be used. If the ITT and the PP analyses yield the same results, the PP will provide supportive evidence of the magnitude of the treatment effect among subjects with different treatment regimens. If the results of the two methods differ, exploratory analyses will be performed to evaluate the factors that may contribute to the differences.

Demographic and baseline data

During the screening visit, for each subject, the following information will be recorded by the investigator:

- ▶ Demography: date of birth, gender, race
- ▶ Medical history (ocular and non-ocular)
- ▶ Vital signs
- ▶ Physical examination
- ▶ Slit lamp examination
- ▶ Fundus examination
- ▶ IOP
- ▶ BCVA

Grading results will be recorded by the Central Reading Centre for the following procedures:

- ▶ SD-OCT
- ▶ CFP
- ▶ FA
- ▶ ICGA

Statistical analysis

Continuous variables will be summarised using the following statistics: number (non-missing sample size), mean, SD, median, IQR, first and third quartiles, minimum and maximum. The number of missing observations will also be reported. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. The number of missing observations will also be reported.

For the primary efficacy analysis following the ITT principle, the full analysis set that include all randomised subjects at week 16 will be used. Missing data will be treated by using last observation carried forward (LOCF).

The safety analysis set will include all subjects who receive any IVA.

Statistical analyses will be performed with STATA version 12.1 (StataCorp, College Station, Texas, USA).

All statistical issues including variables description, tables' contents and statistical methods will be detailed

in the statistical analysis plan that will be finalised before study database lock.

Primary and secondary variables

Primary variables

The primary variables will be defined as:

1. Change in BCVA from Baseline to week 52, that is, BCVA at week 52 minus BCVA at Baseline
2. Polyp regression at week 52 (assessed by ICGA)

Secondary variables

The secondary variables will be defined as:

1. Change in BCVA over time
2. Change in BCVA at week 16
3. BCVA gain ≥ 5 , 10 or 15 letters at week 52
4. BCVA loss ≥ 5 , 10, 15 or 30 letters at week 52
5. BCVA maintenance at week 52 (BCVA change from baseline between -5 and $+5$ letters, exclusively)
6. Polyp regression at week 16, assessed by ICGA
7. Complete polyp regression at week 52, assessed by ICGA
8. Complete polyp regression at week 16, assessed by ICGA
9. Presence of active polyp at week 52, assessed by ICGA
10. Presence of active polyp at week 16, assessed by ICGA
11. Presence of leakage based on fluorescein angiography (FA) at week 52
12. Change in the subfield CRT over time (assessed by spectral domain optical coherence tomography (SD-OCT))
13. Presence of fluid assessed on SD-OCT at week 52
14. Total number of treatments with aflibercept
15. Total number of treatments with verteporfin PDT
16. Frequency and severity of ocular and non-ocular AEs over time

Morphological variables assessed by the Central Reading Centre (based on SD-OCT, CFP, FA and ICGA) will be defined in the SAP.

Statistical hypothesis, model and methods

A descriptive analysis will be conducted to all study variables. Continuous variables will be summarised using the following statistics: number (non-missing sample size), mean, SD, median, IQR, first and third quartiles, minimum and maximum. The number of missing observations will also be reported. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. The number of missing observations will also be reported.

Demographic and baseline data will be described using the descriptive measures defined above and according to each variable type.

Two analyses will be performed for the primary objective considering the two primary outcomes, change in BCVA from baseline to week 52 and polyp regression at week 52.

A two-way factorial analysis of variance (ANOVA) with treatment group and need of PDT as fixed factors will be used to assess the difference between treatments, aflibercept associated with vPDT and aflibercept associated with sPDT, for the change in BCVA from baseline to week 52. The following null (H_0) and alternative (H_1) hypotheses will be considered:

- ▶ $H_0: \mu_1 = \mu_2$
- ▶ $H_1: \mu_1 \neq \mu_2$

where μ_1 is the mean change in ETDRS letter score from baseline to week 52 in treatment group aflibercept associated with vPDT and μ_2 is the mean change in ETDRS letter score from baseline to week 52 in treatment group aflibercept associated with sPDT.

For the polyp regression at week 52, a two-way factorial ANOVA with treatment group and need of PDT as fixed factors will also be used to assess the difference between treatments, aflibercept associated with vPDT and aflibercept associated with sPDT. The following null (H_0) and alternative (H_1) hypotheses will be considered:

- ▶ $H_0: \mu'_1 = \mu'_2$
- ▶ $H_1: \mu'_1 \neq \mu'_2$

where μ'_1 is the mean difference of the total area of polyps from baseline to week 52 in treatment group aflibercept associated with vPDT and μ'_2 is the mean difference of the total area of polyps from baseline to week 52 in treatment group aflibercept associated with sPDT.

Statistically significant results for the primary endpoints will be considered if one of the tests reached a significant level of 0.025.

For the secondary objectives, an exploratory analysis will be performed, particularly for the evaluation of the potential benefit, based on the secondary outcomes, of vPDT compared with sPDT in patients with PCV treated with aflibercept under a T&E regimen.

The different secondary variables will be analysed in both treatment groups.

The number of injections will be tabulated separately for subjects that received aflibercept and for subjects that received aflibercept associated with PDT in both treatment groups.

The proportion of subjects who never needed PDT will be analysed for both treatment groups.

Due to the small sample size, non-parametric tests may be used.

All statistical issues including variables description, tables' contents and statistical methods will be detailed in the SAP that will be finalised before study database lock.

Levels of significance/adjustments

The significance level assumed for the final analysis will be adjusted according to the analyses performed. For the primary analysis, the p value will be adjusted to 0.025 for the two primary variables.

Missing values/censoring/discontinuations/outliers

Due to the small sample size, the LOCF method will be used.

Interim analysis

No interim analysis is planned. If during the study an interim analysis is required, due to safety, efficacy or only for monitoring purposes, this analysis will be masked for the PDT treatment and described in the SAP.

Reporting deviations from the planned statistical analysis

Deviations from the planned statistical analysis will be reported and justified in the final study report.

Safety analysis

For the safety analysis, only treatment-emergent AEs will be considered (eg, AEs with onset after the start of the particular treatment or AEs present prior to the treatment but with increased severity). The number and percentage of subjects reporting AEs will be presented. The IOP measurements will be analysed descriptively including changes from baseline.

Access to source data/documents

Before study initiation or at the baseline visit, the study documents, including the protocol and CRF will be reviewed with the investigators and their staff.

During the study, the following parameters will be checked (in accordance with the MP): (1) completeness of subject records; (2) accuracy of entries on the CRF; (3) adherence to the protocol and to good clinical practices; (4) progress of the enrolment; (5) storage, dispensing and accounting of the study medication according to specifications.

The principal investigator should give the monitor access to the relevant source documents (relevant to check the compliance of the clinical protocol) to confirm their consistency with the CRF entries. Monitoring standards require verification of the presence of informed consent, adherence to the inclusion/exclusion criteria, report of SAEs and the recording of data that will be used for efficacy and safety variables. No information in source documents about the identity of the subjects will be disclosed.

Quality control and quality assurance

Designated investigator staff must enter the information required by the protocol into the CRF.

The principal investigator should ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the principal investigator should keep an enrolment log with confidential identifying information that corresponds to the subject numbers. All documents submitted from the clinical sites will identify the subject exclusively by number. No other personally identifying information should be transmitted.

Monitors will review the CRF for completeness and accuracy and instruct clinical site personnel to make any

required corrections or additions. Queries are sent to the clinical site. Designated clinical site staff is required to respond to the query and clinical site will make the necessary changes to the data.

Data clarifications and/or additions are documented and are part of each subject's CRF. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and data will be made available for data analysis.

Ethics and dissemination

Ethical considerations

Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive No 2001/20, US Code of Federal Regulations Title 21 and Japanese Ministry of Health, Labour and Welfare) and with the ethical principles laid down in the Declaration of Helsinki. The study received approval from the IRB— *Comissão de Ética para a Investigação Clínica* (CEIC), the Portuguese National Ethics Committee for Clinical Research (<http://www.ceic.pt>) and *Comité Ético de investigación Clínica del Hospital Universitari de Bellvitge*.

Informed consent procedures

Subjects should only perform any of the study procedures after providing written (witnessed, where required by law or regulation) IRB/IEC approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. The process of obtaining informed consent should be documented in the subject source documents.

The investigator must ensure that each subject is fully informed about the nature and objective of the study and possible risks associated with participation. Subject should indicate assent to participate in the study by personally signing and dating the written informed consent form. The investigator will retain the original of each subject's signed informed consent form and he will give a copy to the subject.

Amendments may require informed consent form and/or other study-related material revision. If the informed consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent form.

Responsibilities of the investigator

The protocol and the informed consent form must be reviewed and approved by the regulatory authorities before study start. The protocol must be reviewed and approved by the CA and IRB/IEC and informed consent form must be reviewed and approved IRB/IEC and CA if applicable. A signed and dated statement that the protocol and informed consent have been approved by the national regulatory authorities must be given to the sponsor before study initiation. Prior to the start of the study, the principal investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to study monitors, auditors and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authorities, the investigator must inform the sponsor immediately that this request has been made.

The principal investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The principal investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training and experience.

Data handling and record keeping

The principal investigator must maintain up-to-date source documents for each subject, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject.

The principal investigator must keep study records and source documents during at least 10 years according to internal procedure of the sponsor or superior to comply with national law.

If for any reason the principal investigator withdraws from the responsibility of keeping the study records, custody must be transferred to the sponsor.

Financing and insurance

This is an Investigator Driven Clinical Trial. Financial support will be given to the clinical sites according to the Clinical Trial Agreement that will be signed with the sponsor to perform the clinical study.

As required by the national law, the sponsor will provide insurance for the clinical trial to cover any subject injuries related with the clinical trial procedures and/or treatments.

Publication policy

On study completion and finalisation of the study report, the results of this trial will be submitted for publication

at a peer-reviewed journal. Also, the study results will be presented at local and international congresses with the intention to share the new scientific data with our peers. The publication policy will be described in the Clinical Trial Agreement.

Protocol

Protocol adherence

Investigators ascertain that they will apply due diligence to avoid protocol deviations. If the investigator believes that a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment is agreed on by the sponsor and approved by the CA and IRB/IEC, it cannot be implemented.

Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, the CA and IRB/IEC. Only amendments that are required for subject safety may be implemented prior to regulatory authorities approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the regulatory authorities should be informed within 10 working days.

Amendments may require informed consent form and/or other study-related material revision. If the informed consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent form.

Author affiliations

¹Association for Investigation and Biomedical Research on Light and Image (AIBILI), Coimbra, Portugal

²Faculty of Medicine, University of Coimbra (FMUC), Coimbra, Portugal

³Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal

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Competing interests We have read and understood BMJ policy on declaration of interests and declare the following interests: RS is a consultant for Alcon; Alimera Sciences; Allergan; Bayer; Novartis and THEA.

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