BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050252
Article Type:	Protocol
Date Submitted by the Author:	18-Feb-2021
Complete List of Authors:	Vyas, Chinmayi; Singapore National Eye Centre Cheung, Chui Ming Gemmy; Singapore National Eye Centre, Medical Retina Tan, Colin; Tan Tock Seng Hospital Chee, Caroline; National University Hospital Department of Ophthalmology Wong, Kelly; Singapore Eye Research Institute Wong, Tien; Singapore Eye Research Institute, ; Singapore National Eye Centre, Jordan-Yu, Janice; Singapore Eye Research Institute Tan, Anna; Singapore National Eye Centre, Ophthalmology Fenner, Beau; Singapore National Eye Centre Sim, Shaun; Singapore National Eye Centre Teo, Kelvin Yi Chong; Singapore National Eye Centre, ; Singapore Eye Research Institute, Medical Retina
Keywords:	Medical retina < OPHTHALMOLOGY, Clinical trials < THERAPEUTICS, Medical ophthalmology < OPHTHALMOLOGY

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A multi-center, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy

Chinmayi Himanshuroy Vyas [1] ,Chui Ming Gemmy Cheung [1,2] ,Colin Tan Siang Hui [2,3]
Chee Ka Lin Caroline[4], Kelly Wong Kai Li[1], Janice Marie Jordan-Yu[1]Tien Yin Wong[1,2]
Anna Cheng Sim Tan[1,2], Beau James Fenner[1], Shaun Sebastian Sim[1], Kelvin Yi Chong Teo [1,2]

1. Singapore Eye Research Institute, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751, Singapore
2. Duke-NUS Medical School, National University of Singapore, Singapore
3. National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore, Republic of Singapore
4. National University hospital, Singapore, Republic of Singapore.

Correspondence to :

Dr Kelvin Yi Chong Teo [1,2]
Consultant
Singapore Eye Research Institute, Singapore National Eye Centre
11 Third Hospital Avenue, Singapore 168751
Email : kelvin.teo.y.c@singhealth.com.sg
Telephone: + 65-6227 7266
Fax: + 65-6227 7291

Key words:
Medical retina, Clinical trials , Ophthalmology , polypoidal choroidal vasculopathy, intravitreal aflibercept, photodynamic therapy

Financial support : Financial support is provided by National Medical Research Council (NMRC) Singapore open fund large collaborative grant , NMRC/LCG/004/2018

Competing interests : The authors have no relevant financial or non-financial competing interests in any material discussed in this manuscript

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ABSTRACT

Purpose: To compare the efficacy and safety of intravitreal aflibercept monotherapy (IVA) vs aflibercept combined with reduced fluence PDT (IVA + RF-PDT) for the treatment of polypoidal choroidal vasculopathy (PCV)

Methods and analysis:
Multi-centred, double-masked, randomised controlled trial to compare the 2 treatment modalities. The primary outcome of the study is to compare the 52-weeks visual outcome of IVA vs IVA + RF-PDT. One hundred and sixty treatment-naïve patients with macular PCV confirmed on Indocyanine green angiography (ICGA) will be recruited from three centres in Singapore. Eligible patients will be randomized (1:1 ratio) in to one of the following groups: IVA monotherapy group- aflibercept monotherapy with sham photodynamic therapy (n=80); combination group - aflibercept with reduced fluence photodynamic therapy (n=80); Following baseline visit, all patients will be monitored at 4-weekly intervals during which disease activity will be assessed based on Best corrected visual acuity (BCVA), ophthalmic examination findings, optical coherence tomography (OCT) and angiography where indicated. Eyes that meet protocol-specified retreatment criteria will receive IVA and sham/RF-PDT according to their randomization group. Primary endpoint will be assessed as change in BCVA at week 52 from baseline. Additional endpoints will include anatomical changes based on OCT, OCT angiography (OCTA) and dye angiography, as well as safety assessment.

Ethics and Dissemination:
This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the ICH E6 guidelines of Good Clinical Practice and the applicable regulatory requirements. Approval from the Singhealth centralised institutional review board has been sought prior to commencement of the study.

Strength and limitations of this study

- The first randomized clinical trial conducted to compare the efficacy of IVA vs IVA + RF-PDT in an Asian population.
- The benefit of baseline RF-PDT which may reduce the injection treatment burden, has not been formally evaluated in combination with aflibercept

- OCTA findings will be prospectively collected at every visit and included in the analysis.
- Multicenter randomized clinical trial conducted in tertiary eye setup with masked image grading by independent ophthalmology reading center.
- One limitation to consider would be the lack of head-on comparison between full fluence and reduced fluence PDT.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular Age related macular degeneration (nAMD) which comprises up to 50 % of exudative maculopathy in the Asian population.[1–5] Anti-vascular endothelial growth factor (anti-VEGF) therapy has been established as the standard of care for treatment of nAMD,[6–9] however the response in eyes with PCV has been less consistent.[10–13] Current best evidence for the treatment of PCV comes from two recent randomized controlled trials. The EVEREST II study reported superior visual gains and lower number of anti VEGF treatments in the intravitreal ranibizumab combined with PDT (IVR+PDT) arm compared to IVR monotherapy.[14,15] On the other hand, the PLANET study reported good visual gain (>10 letters) in the IVA monotherapy arm, and demonstrated no additional benefit of IVA with rescue PDT.[16,17] Hence both approaches are currently practised. However, there remains a gap in the evidence which is specific to aflibercept. Despite the impressive visual gain with IVA monotherapy, limited polyp closure rate was achieved with IVA monotherapy. The lower rate of polyp closure without the use of PDT in combination with anti VEGF therapy remains an area of concern clinically as unclosed PL may require regular long term treatment or increase risk of recurrence and haemorrhage.[18] There have been no randomized controlled trials to-date to evaluate whether addition of PDT to IVA would result in superior visual and/or polyp closure compared to IVA monotherapy.

Here we report the methodology of a study designed to evaluate the efficacy and safety of combination IVA and PDT in patients with PCV. We hypothesize that the combination group will achieve comparable visual outcomes, higher polyp closure rate with lower number of retreatments compared to IVA monotherapy. In addition, this study will use RF-PDT, which has been reported to have a better safety profile compared to

full-fluence PDT.[19,20] Finally, this protocol will incorporate the analysis of novel imaging biomarkers, such as choroidal features like choroidal vascular hyperpermeability (CVH)[21,22] and choroidal vascularity index (CVI).[23] Specifically OCTA will be performed during every study visit, thus allowing for longitudinal analysis within a RCT setting.

METHODS AND ANALYSIS

Study type and study design

Multi-centred randomised controlled trial registered with Clinical trial.gov (http://clinicaltrials.gov/show/ NCT03941587). The trial registration dataset in accordance with world health organisation (WHO) is summarized in supplementary Table 1.

Protocol Number: R1735/58/2020

Protocol version : 1.1/ 02 October 2020

Study title

A multi-centre, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy

Principle investigator

Prof Gemmy Cheung Chui Ming, FRCS*Ophth*

Singapore Eye Research Institute

Study Setting:

Site 1: Singapore National Eye Centre

Contact: Prof Gemmy Cheung Chui Ming

Site 2: National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore

Contact : A/Prof Colin Tan

Site 3: National University hospital, Singapore.

Contact : A/Prof Caroline Chee

Central Reading Centre

Singapore National Eye Centre Ocular Reading Centre (SORC)

Study outcome

Primary outcome

The primary outcome of this study is to compare the change in BCVA from baseline to week 52 between the monotherapy group (IVA) and the combination group (IVA + RF-PDT)

Secondary outcomes

The secondary visual outcomes are:

Final BCVA at week 52

Proportion of eyes with gain >= 5,10,15 letters at week 52

Proportion of eyes with loss >= 5,10,15 letters at week 52

Proportion of eyes with 70 or more logMAR letters

Comparison of secondary visual outcomes between groups

The secondary anatomical outcomes are:

To compare anatomical outcomes at week 12 and 52 between treatment groups (assessed by multimodal imaging).

The secondary management outcomes are:

Total number of intravitreal injection of Aflibercept and RF-PDT treatment

Retreatment number of intravitreal injection of Aflibercept and RF-PDT treatment

Exploratory imaging analysis :

Imaging predictors CVI, CVH and sub RPE hyperreflective ring

Longitudinal changes in OCTA between the groups

Outcome definitions

Visual assessment of BCVA will be determined according to the logMAR letters in all visits

Polyp closure will be defined as a polyp disappearance as assessed by investigators and reading centre on ICGA

Efficacy assessment

All efficacy assessment include both functional and anatomical evaluation. These include comparison of following between the groups: BCVA, Polyp closure on ICGA, presence of intralesional or sub-lesional fluid on SD-OCT and OCTA.

Safety assessment

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

Time line

A total of 180 PCV patients recruited over approximately 16 months period (starting Feb 2021) total follow up time of 52 weeks after inclusion.

Sample selection

The study population will consist of a group of adults aged 50 and above with symptomatic macular PCV who are naïve to treatment in the study eye. Study participants can only have one study eye. If both eyes are eligible for the study, the eye without previous intravitreal anti-VEGF treatment will be selected. If both eyes are treatment naïve, the eye with worse VA should be selected as the study eye. There will be no restriction of recruitment according to the race of the patient.

Eligibility criteria

Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For potential study participants who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the potential study participant by a study investigator and study coordinator. The potential study participant will be given the informed consent form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study.

Inclusion criteria

- Male or female study participant aged >= 50 years old at the time of informed consent.
- Best corrected visual acuity early treatment diabetic retinopathy study (ETDRS) letters score of 4 to 73 letters (Snellen equivalent approximately 20/32 to 20/800) in the study eye.
- Confirmed diagnosis of symptomatic macular PCV based ICGA with activity of PCV confirmed by exudation involving the macula on OCT or FA or both.
- Presence of intra retinal or subretinal fluid/blood at the fovea as seen on OCT
- Treatment naïve
- *NO previous treatment with intravitreal anti-VEGF agents, regardless of the indication
- *NO previous thermal laser in the macular region, or verteporfin photodynamic therapy , regardless of indication
- *NO other previous treatment for nAMD, except oral supplements and traditional Chinese medicine
- Greatest Linear Dimension (GLD) of the total lesion area - Branching Vascular Network (BVN) + polyps < 5400µm (~9 MPS Disc Areas) as delineated by ICGA.
- Able and Willing to provide written informed consent and comply with all scheduled visits and study procedure.

Exclusion criteria

Participant

- Medical condition that, in the opinion of the investigator, would preclude participation in the study (e.g. unstable medical status including blood pressure, cardiovascular disease, and glycaemic control).

- Participation in an investigational trial within 30 days of enrolment which involves treatment with unapproved investigational drug.
- Known allergy to any component of the study drug.
- Blood pressure > 180/110 (systolic above 180 OR diastolic above 110 on repeated measurements). If blood pressure is brought below 180/110 by anti-hypertensive treatment, individual can become eligible.
- Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 4 months prior to randomization.
- Systemic anti-VEGF or pro-VEGF treatment within four months prior to randomization or anticipated use during the study.
- Amblyopia or blind in one eye

Study Eye

- Eye with intra retinal or subretinal fluid due to other causes than PCV
- An ocular condition is present (other than PCV) that, in the opinion of the investigator, might affect intra or sub retinal fluid or alter visual acuity during the course of the study (e.g., DME, vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.)
- Substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by more than three lines (i.e., cataract would be reducing acuity to worse than 20/40 if eye was otherwise normal).
- Any intraocular surgery within 3 months of enrolment
- Treatment with intra-vitreal corticosteroids
- History of retinal detachment or surgery for retinal detachment
- History of vitrectomy
- History of macular hole
- Evidence of vitreomacular traction that may preclude resolution of macular oedema > 4 disc areas of intra/sub retinal haemorrhage
- Aphakia
- Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis

Other Eye

- Active intraocular inflammation

- History of uveitis

Patient withdrawal

Participants may voluntarily withdraw from the study at any time. If a study participant is considering withdrawal from the study, the principal investigator should personally speak to the individual about the reasons, and every effort should be made to accommodate him or her.

Study participants who withdraw will be asked to have a final closeout visit at which the testing described for the protocol visits will be performed. Study participants who have an adverse effect attributable to a study treatment or procedure will be asked to continue in follow-up until the adverse event has resolved or stabilized.

Study assessment and visit schedule/ study procedures/ data acquisition

Screening evaluation and baseline testing

Historical Information

A history will be elicited from the potential study participant and extracted from available medical records. Data to be collected will include: age, gender, ethnicity and race, past medical history and medications being used, as well as ocular diseases, surgeries, and treatment.

Baseline Testing Procedures

- The following procedures are needed to assess eligibility and/or to serve as baseline measures for the study.
- Best-corrected Visual Acuity: BCVA will be measured using the ETDRS VA protocol following manifest refraction.
- Optical Coherence Tomography/ OCT Angiography: OCT and OCTA will be performed. Both standard and enhanced depth imaging scans will be performed.
- Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated fundus examination (within 21 days prior to randomization).
- Blood pressure measurements
- Fundus Photography, Autofluorescence photography
- Fundus fluorescein and Indocyanine Green angiography: FFA and ICGA will be performed.
- Study participants will be randomized to 2 treatment groups using a ratio of 1:1 (combination group: aflibercept combined with RF-PDT, IVA monotherapy group: Aflibercept monotherapy with sham RF-PDT)(Figure 1)

Disease characteristics of the study eye assessed by the investigator at screening (Day 1):

- Diagnosis of PCV based on ICGA
- Polyp presence will be defined as the presence of single or multiple hyperfluorescent lesions on ICGA within the first 6 min with one or more of the following features:
- Nodular appearance on stereoscopic view of ICGA
- Hypo-fluorescent halo surrounding the focal hyperfluorescent lesion(s) on early frames
- Pulsatile filling of the lesion on video ICGA
- Presence of activity clinically as evidence by presence of haemorrhage, oedema on fundus examination.
- Presence of activity as evidence by intra retinal or sub retinal fluid on OCT

Follow-up visit schedule and examination

At each visit, study participants will be assessed based on best corrected visual acuity (BCVA), ophthalmic examination, OCT and OCT-angiograph (OCT-A). (Table 1)

In addition, colour photography, autofluorescence photography, fluorescein and indocyanine green angiography will be performed at baseline, week 12 and week 52. (Table 1)

Additional investigations at interim visits may be performed at the discretion of the investigator if there is evidence of disease activity. (Figure 2)

Qualification for retreatment with Aflibercept (Figure 3) (week 4 to week 48) will be based on signs of disease activity defined as persistent intraretinal or subretinal fluid on OCT and BCVA.

Qualification for retreatment with PDT (Figure 3) (week 4 to week 48, repeated not more frequently than 12 weeks apart) will be based on signs of persistent polyps on ICGA, according to randomization group.

End of study visit

At week 52, all subjects will return for end of study visit. All subjects will be assessed based on BCVA, ophthalmic examination, FA, ICGA, colour fundus photography, Autofluorescence and OCT and OCT-A

Role of centralised reading centre

All eligibility criteria and retreatment decisions will be based on investigators assessments. All images will be sent to the SNEC ocular reading centre (SORC) at the conclusion of the clinical study for the purpose of analysis. These gradings will have no bearing on the retreatment decisions during the trial. Grading protocol is included as a supplementary table 2.

Treatment procedure

Study eyes will receive either intravitreal injection of aflibercept along with sham RF-PDT or RF- PDT depending on the assigned randomization group. (Figure 1)
When a patient's condition warrants treatment with both RF-PDT/ sham RF-PDT and Aflibercept, sham/ RF-PDT will be performed first.

Intravitreal Injection Technique
Antibiotics in the pre-, peri-, or post-injection period are not necessary but can be used at investigator discretion if such use is part of his/her usual routine.

Prior to the injection, the study eye will be anaesthetized with topical anaesthetic, followed by a povidone iodine prep of the conjunctiva. (Instil 5% povidone iodide on to the ocular surface and allow adequate time prior to injection)

Aflibercept will be withdrawn using aseptic technique through an 18-guage filter needle attached to a 1-ml syringe. The needle will be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The needle should be replaced by a sterile 30-guage needle for the intravitreal injections. The contents of the syringe should be expelled until the plunger is aligned with the line that marks 0.05ml on the syringe.
The injection will be performed using sterile technique. Investigator will use a surgical hand disinfection technique and wear sterile gloves. Periocular skin and eyelid margins and eye lashes will be cleaned with 10% povidone iodine.

Skin will be dried and drape will be applied. Investigator will insert eyelid speculum, ensuring that it is well positioned underneath the eyelids to direct the eyelashes away from the field. Callipers should be used to mark the injection site. The entry site of the needle should be 3.0- 3.5 mm from the limbus in pseudophakic patients, and 3.5-4.0 mm in phakic patients.
The conjunctiva may be displaced anteriorly using either forceps or cotton tipped applicator so that no direct route between vitreous and ocular surface remains. The needle is inserted perpendicular through sclera with the tip aimed towards the centre of the globe (to avoid any contact with the posterior lens capsule)
IOP measurement post-injection is not mandatory. While small volume injections (0.05ml) are unlikely to cause IOP rise, it should be considered in participants with ocular hypertension or glaucoma, and in all cases where participants are symptomatic for pain or reduced vision immediately following injection. Should a high intraocular pressure resulting in non-perfusion of the central retinal artery occur, indicated by no perception of light (NPL) in the treated eye, an anterior chamber paracentesis is indicated. Such decompression needs to be achieved within 3-5 minutes. Participants should be instructed to report any symptoms regarding eye pain or discomfort, increased redness of the eye, or

additional blurring of vision (which may indicate endophthalmitis) to the treating ophthalmologist without delay

Delay in Giving Injections

If a scheduled injection is not given on the day of study visit, it may be administered within 7 days after the occurrence of the study visit. If it is not given by that time, it will be considered missed. If an injection is given late, the next scheduled injection should occur no sooner than 28 days after the previous injection.

Non-Study Eye Injections

If the non-study eye is going to be treated for any condition which requires treatment with an anti-VEGF agent, it may be treated at the discretion of the investigator. Treatment of the fellow- eye with aflibercept is possible.

RF-PDT/ Sham RF-PDT administration

Pre-treatment patient preparation

The verteporfin (Visudyne) / sham (5% dextrose in water solution for infusion) intravenous infusion will be administered using standard aseptic technique. The skin at the infusion site will be disinfected prior to the infusion as per local standard.

This intravenous procedure will be done using the same cannula inserted into patient for FFA/ICG procedure. There will be no additional insertion of cannula. During the infusion, the delivery syringe and intravenous line should be wrapped in aluminium to mask the identity of treatment. The active RF-PDT/ Sham RF-PDT will be performed by an unmasked investigator enrolled of the study team.

Active RF-PDT

Verteporfin will be administered according to the current Visudyne package labelling. A dosage calculated at 6mg/m2 body surface area in a 30-ml solution will be infused intravenously over a 10-minute period. Fifteen minutes after the start of the infusion (verteporfin), the study eye will be anaesthetized with topical anaesthetic and a contact lens will be used for the laser procedure. Laser light will be applied to the study eye for 83 seconds with the following parameters: Light dose (reduced fluence) 25 J/cm2, Light wavelength 689 nm

Sham RF-PDT

The sham infusion will be prepared with 5% dextrose in water solution for infusion. A 30 mL volume of this solution will be infused intravenously over a 10-minute period to mimic the verteporfin infusion.

Fifteen minutes after the start of the infusion (sham solution), the study eye will be anaesthetized with topical anaesthetic and a contact lens will be used for the laser procedure. A sham laser (i.e. a true laser light will not be used) procedure that will mimic the procedure of the active RF-PDT will performed

Post treatment care

Patients who receive RF-PDT will become temporarily photosensitive after the infusion. All patients who receive verteporfin RF-PDT/ sham RF-PDT will be instructed to avoid direct sunlight for 48 hours.

Treatment Regimen Adjustments

If the study eye develops a treatment-related adverse event at any time during the study, treatment dose may be temporarily held and the reason for dose holding will be recorded in the CRF.

The treatment regimen will be adjusted based on the following criteria:

• Intraocular inflammation: may hold dose at the investigator's discretion, eg, if intraocular inflammation is >= 2+ in the study eye. Treatment may resume when the inflammation has resolved.

• IOP: hold dose if IOP is >= 30 mm Hg in the study eye. Treatment may resume when IOP is <= 30 mm Hg, either spontaneously or by treatment, as determined by evaluating physician.

• New retinal break or retinal detachment: hold dose for the study eye. Treatment may resume after the retinal break/detachment had been successfully treated.

• Ocular and/or periocular infection: hold dose until the infection is resolved in both eyes.

The investigator may hold or discontinue study treatment for other safety reasons at his/her discretion.

Randomization and blinding

Study participants will be randomized to 2 treatment groups using a ratio of 1:1(combination group: aflibercept combined with RF-PDT, IVA monotherapy group: Aflibercept monotherapy with sham RF-PDT)(Figure 1) and randomization will be performed using a blocked randomization method. Each site will be randomized to a 1:1 ratio for each study treatment arm.

The site at the Singapore national eye centre (SNEC) will be randomized in blocks of 20 and the remaining 18 participants will be randomized in blocks of 9. For the Tan Tock Seng Hospital (TTSH) site, 30 participants will be randomized in blocks of 10. For the National University hospital (NUH) site, 32 participants will be randomized in block of 20, with the remaining 12 participants randomized in blocks of 6.

Blinding : Initial assessment and recruitment of the patient will be done by the masked Co- investigator and Masked Research co-ordinators. The treatment procedure will be done by the unmasked co-Investigators. Both participants and masked team will be masked to treatment received.
Unblinding will be permissible only in circumstances involving SAE.

Study completion

All participants that have completed 52 weeks of treatment are considered to have completed the study successfully.

Treatment schedule

Treatment randomization is summarized in Figure 1.
All participant with macular PCV will be assessed at baseline and randomized to each study treatment arm (combination group: aflibercept combined with RF-PDT, IVA monotherapy group: Aflibercept monotherapy with sham RF-PDT)
At the baseline visit, depending on the randomization the combination group will receive IVA and RF-PDT while the monotherapy group with receive IVA + sham PDT.
After baseline visit, patients will be monitored at 4 weekly interval between week 8 and 48
At each study visit, disease activity will be assessed by masked investigator. If disease activity is present according to the prespecified treatment protocols (figure 3), patients will be treated according to randomisation arm. All clinical evaluations during study visits will be carried out by the masked investigator while treatment administration will be undertaken by the unmasked investigator.

Study medication

Aflibercept (EYLEA): study eyes will receive a dose of 2mg in 0.05 ml of aflibercept

Verteporfin RF-PDT/ Sham RF-PDT: Verteporfin will be administered according to the current Visudyne package labelling. A dosage calculated at 6mg/m2 body surface area in a 30-ml solution will be infused intravenously over a 10-minute period. Fifteen minutes after the start of the infusion (verteporfin), the study eye will be anaesthetized with topical anaesthetic and a contact lens will be used for the laser procedure. Laser light is applied to the study eye for 83 seconds with the parameters: Light dose (reduced fluence) 25 J/cm2, Light wavelength 689 nm

Dosage form, packaging and labelling

Aflibercept (EYLEA) is solution for injection, clear, colourless to pale yellow, iso-osmotic solution, pH6.2. following intravitreal injection of 2 mg per eye of the mean Cmax of free aflibercept in the

plasma was noted to be 0.02mcg/ mL(range :0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free aflibercept plasma concertation was undetectable two weeks post dosing.

Visudyne vial contains 15mg of verteporfin. After constitution, 1 mL contains 2mg of verteporfin. 5mL of reconstituted solution contains 15mg of verteporfin. Information on trial product is detailed in the package insert as attached in Appendix.

Sham RF-PDT consists of dextrose 5% solution followed by light application RF-PDT.

The sham infusion will be prepared with 5% dextrose in water solution for infusion. A 30 mL volume of this solution is infused intravenously over a 10 minute period to mimic the verteporfin infusion.

Storage and drug accountability

Aflibercept (EYLEA) will be stored in a refrigerator at 2°C to 8°C. It will be stored securely in the SERI Pharmacy, SNEC building. It will be monitored by a 24-hour Temperature monitoring System (TMS) and report will be generated on a bio-weekly basis. Alarms to any excursion will be triggered and the designated staff will be informed.

Visudyne will be stored in the original package in order to protect from light, at a room temperature not above 25°C. It will be stored securely in the SERI Pharmacy cabinet with restricted access.

The label on each Aflibercept/ Visudyne/ Dextrose 5% will include short study title, the name and country of origin of the manufacturer, batch number, trial number, expiry date, storage conditions, emergency contacts, subject no/ initials, date of dispensed, visit/ week and the words “For Clinical Trial Use Only”.

Concomitant treatment

Any concomitant medications used by the subject from the date of enrolment until the end of the study except for routine medications given for ocular procedures require by the protocol, i.e fluoresceine, indocyanine, dilating drops and topical anaesthetics should be recorded as concomitant medications including the start and stop dates and indications.

Other non Anti VEGF therapy or intravitreal corticosteroids in the study eye are not allowed.

If the fellow-eye needs treatment for wet AMD (including PCV) , subjects can be treated in accordance to standard of care and continue in the study. All medications (prescription and over the counter), vitamin and mineral supplements, and / or herbs taken by the participant will be documented.

Study completion and poststudy treatment

Last visit will occur at week 52 (+/- 7 days)

No special procedures will be carried out in addition to that stated in the schedule. Participants will not receive any treatment at the study completion visit.

Study participants will continue their routine follow – up with their regular physicians upon completion of the final study. There will be no post study visits planned.

Safety assessment

Parameters

Safety parameters will include assessment of IOP,AE(adverse events) and serious adverse event.

SAE and serious adverse reaction (SAR), are defined as any Untoward medical occurrence or effect that , at any dose result in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is an important medical event.

Adverse event

Adverse events are defined as the following and 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 pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study and 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.

Reporting and follow-up

Reporting of adverse events involves the Principal Investigator submitting to Centralised Institutional Review Board (CIRB) the SAE Reporting Form to CIRB within the stipulated timeframe. The Principal Investigator is responsible for informing the institution representative, the chairman medical board (when required by the institution for local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- Local unexpected SAE resulting in death that are related events should be reported immediately - within 24 hours of the Principal Investigator becoming aware of the event.
- Local unexpected, life-threatening SAE that are related events should be reported as soon as possible but no later than 7 calendar days after the Principal Investigator is aware of the event, followed by a full report within 8 additional calendar days.
- Local unexpected, not life-threatening SAE that are related events, should be reported no later than 15 calendar days after the Principal Investigator is aware of the event.

- An increase in the rate of occurrence of Local expected SAE that are related events, which is judged to be clinically important, should be reported within 15 calendar days after the Principal Investigator is aware of the event.
- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and related should be reported not later than 30 calendar days after the principal investigator is aware of the event. The review will be done on monthly basis for standard aggregate adverse event (AE) safety data report

The following standard aggregate AE safety data reports will be reviewed:

- Number and percentage of enrolled subjects reporting adverse events (AEs) by body system (i.e., primary system organ class) and preferred term in descending frequency order.
- Serious adverse events (SAE) (treatment or procedure related and non-related)- cumulative
- All AEs

The following reports of additional study – specific data will be reviewed

1)Targeted adverse events

- Intraocular inflammation/infection including AC inflammation, uveitis, vitritis, iritis, iridocyclitis, choroiditis, retinal vasculitis and endophthalmitis
- Visual acuity reduced
- Intraocular pressure increase
- Retinal tear
- Retinal detachment
- Vitreous haemorrhage
- Retinal haemorrhage
- Macular scar
- Systemic VEGF inhibition

2) Biomicroscopy/ indirect ophthalmoscopy (by visit per subject)

≥ 2 grade increase in each separate parameter (Corneal edema, Conjunctival hyperemia, Anterior chamber cells, Anterior chamber flare, Keratic precipitates, Vitreous cells, Vitreous flare/haze) and documented changes in vitreous, optic disc and retina from baseline.

3) BCVA ≥ 15 letters decrease from baseline at any visit (by visit per subject)

Data governance and safety

A Data and Safety Monitoring Committee will approve the protocol, template informed consent form, and substantive amendments and provide independent monitoring of adverse events. Cumulative adverse event data are semi-annually tabulated for review by the DSMC. Following each DSMC data review, a summary will be made available for submission to Institutional Review Board. A list of specific adverse events to be reported to the DSMC expeditiously will be compiled and included as part of the DSMC Standard Operating Procedures

Data analysis

Determination of sample size

Assuming a drop out 10% , 80 subjects per treatment arm will be adequate to demonstrate non-inferiority of the combination arm (within a 5-letter non-inferiority margin, alpha=0.025 (one sided), power=0.8), assuming BCVA gain of 11.5 letters in the combination arm vs 10.7 letters in the monotherapy. Furthermore, we will be able to demonstrate superiority of combination over monotherapy arms with a 3-letter superiority difference assuming a BCVA gain of 13.7 letters in the combination arm vs 10.7 letters in the monotherapy (alpha=0.025 (one sided), power=0.8) and assuming a drop out 10%). Furthermore, this same sample size will detect a difference in number of injections of 2 based on reducing from 7.3 in the monotherapy arm vs 5.2 in the combination arm with >99% power (injection numbers are based on EVEREST II study data).

Statistical Methods

For statistical purposes, baseline will be defined as the last available non-missing value collected just prior to the start of treatment in the study eye. For patients with screening assessments but who do not enter the treatment period, data will only be listed. For all patients only one eye will be considered as the study eye, and only for this eye efficacy analysis will be performed. Unless otherwise specified, all statistical tests will be two-sided with a 0.05 level of significance, and all confidence intervals will be two-sided with 95% confidence level.

Categorical variables will be presented as the number and percentage of patients in each category. Continuous variables will be summarized using descriptive statistics (e.g. n, mean, standard deviation, median, minimum, and maximum). Descriptive statistics will be provided for patient demographics and all baseline characteristics. Relevant medical history and current medical conditions will be tabulated by system organ class and preferred term of the MedDRA dictionary. Separate tables will be provided for ocular and non-ocular histories and conditions. Full analysis set (FAS) comprises all patients to whom treatment regimen has been assigned.

Intent-to-treat (ITT): patients will be analysed according to the treatment regimen they are assigned to at randomization. No data will be excluded from the FAS analyses because of protocol deviation. All efficacy evaluations will be carried out on the FAS.

Per protocol Set (PPS) will consist of all patients in the FAS who followed the treatment regimen as randomized and completed Week 24 without clinically significant protocol deviations.

Primary efficacy evaluation will be carried out on both the FAS and the PP set. The primary variable is the change in BCVA at Week 52 compared to baseline. The primary analysis will be performed on the FAS using the LOCF approach for imputing missing data. The statistical testing will be carried out using paired t-test. The analysis will be repeated for the PP set using the same model.

Analysis of secondary endpoints will focus on the study eye only and will be based on the FAS. At all the time points assessed, each efficacy variable will be presented graphically and descriptive statistics provided based on absolute values and changes from baseline. For continuous and ordered categorical variables, changes from baseline will be compared between treatment groups using ANOVA.ANCOVA models/ t-test and stratified/unstratified Cochran-mantel-Hansel tests. Stratification will follow the approach described for the primary analysis as applicable. Logistic regression will be used for analyses of binary endpoints.

Primary and secondary variables

Primary variables

Change in BCVA baseline to week 52 : BCVA at week 52 minus BCVA at baseline, Loss of ≥ 5 letters from Best Corrected Visual Acuity since baseline

Secondary variables

- Final BCVA at week 52
- Proportion of eyes with gain >= 5,10,15 logMAR letters at week 52
- Proportion of eyes with loss >= 5,10,15 logMAR letters at week 52
- Proportion of eyes with 70 or more logMAR letters at week 52
- Proportion of eyes with polyp closure at week 12 and 52 assessed by ICGA
- Proportion of eyes with Presence of intraretinal and sub-retinal fluid at week 12 and 52 as evidence by OCT
- Mean number of intravitreal injections of aflibercept and RF-PDT
- Frequency and severity of ocular and non-ocular adverse events over 52 weeks
- Evaluate the influence of anatomical Imaging predictors such as CVI, CVH and sub RPE hyperreflective ring at week 12 and 52 between treatment groups (assessed by multimodal imaging).
- Longitudinal changes in OCTA between the groups

Reporting study deviations from the planned statical analysis

Deviations from the planned statical analysis will be reported in the final study report

Safety analysis

Only treatment-emergent AEs will be considered. The number and percentage of subjects reporting AEs will be reported

Access to source data/documents

Case report files (CRFs) will be reviewed with the investigators study team before study initiation and baseline visit. During the study , the following parameters will be ascertained
1)completeness of the records 2) accuracy of entries 3) adherence to the protocol and good clinical practices 4) progress of the enrolment 5) storage, dispensing and accounting of the study medications

source documentations will be available for monitoring and audit for compliance with clinical protocol. Monitoring standards require verification of presence of informed consent, adherence to the inclusion /exclusion criteria , report of SAEs and recording of data that will be used for efficacy and safety variables. Source documentation should not contain any participant identifiers .

Ethics and dissemination

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

Regulatory and ethical compliance

The investigator(s) and institution(s) will permit and facilitate all study related monitoring audit(s) and regulatory review(s) and inspection(s), providing direct access to source data/ documents.

Informed consent procedures

Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be

obtained. For potential study participants who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the potential study participant by a study investigator.

The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study.

Responsibilities of the investigator

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement

Data handling and record keeping

Research data will be anonymized as soon as possible and both identification key and the de-identified data will store in separate folders in the institution access-controlled shared folders. Case files will be kept under lock and key, with restricted access to the key, as defined within the study delegation log. The study data will be stored for at least 15 years and then destroyed or deleted.

Patient and public involvement

Patients are not invited to comment on the study design and are not consulted to develop patient relevant outcomes or interpret results. Patients are not invited to contribute to the writing or editing of this document for reliability or accuracy.

Conflicts of interest

None for any authors related to the design , execution and reporting of this study

Financing and insurance

Financial support is provided by national medical research council Singapore open fund large collaborative grant and covered under national clinical trial insurance policy.

Roles and responsibilities : contributor ship

GCMG and KYCT conceived the study. GCMG and KYCT initiated the study design and helped with implementation. GCMG is the grant holder. KYCT provided statistical expertise in clinical trial design. All authors contributed to refinement of the study protocol and approved the final manuscript.

Roles and responsibilities of sponsor and funder

This funding source had no role in the design and conduct of this study and will not have any role during its execution, analysis , interpretation of data or decision to submit results

Trial sponsor: Singapore Eye Research Institute / Singapore National Eye Centre

Reference : SERI Ref. No. R1735/58/2020

Address :11 Third Hospital Avenue, Singapore 168751, Singapore

Publication policy

On study completion and finalisation of the study report the results of this trail will be submitted for publication in accordance to institutional publication policy of Singapore Eye Research Institute / Singapore National Eye Centre

Protocol adherence

Investigators ascertain that they will apply due diligence to adhere to the study protocol and avoid protocol deviations

Protocol amendments

Change and addition to the protocol can only be made in written protocol amendment that must be approved by the CIRB. Amendments will required informed consent forms and/or other study- related material revision. If with informed consent form revision all subject enrolled in the study must sign the approved, revised informed consent form.

DISCUSSION

The EVEREST II and PLANET studies have demonstrated that both anti-VEGF monotherapy and combination of anti-VEGF with PDT can achieve positive visual outcomes in eyes with PCV.[14–17] In the EVEREST II study, the combination (IVR +PDT) group achieved superior visual gain compared to the monotherapy (IVR) group (+7 vs +5 letters gain) with on average 2 less IVR injections over 1 year.[14,15] In the PLANET study, both monotherapy arm (IVA) and IVA with rescue PDT arm achieved >10 letters improvement at 1 year and no benefit from rescue PDT was demonstrated.[16,17] Almost 78% of eyes achieved a fluid free retina after the initial three loading doses of IVA. The EVEREST II study, however, showed a significantly higher polyp regression in the combination arm compared to IVR monotherapy (69.7% vs 33.8%).[14] The polyp closure rate reported in the PLANET study was 38.9% for the IVA monotherapy and 44.8% for IVA with rescue PDT arm.[16] To-date, there are still no studies evaluating whether combination of IVA with PDT at baseline may achieve favourable visual and anatomical outcomes compared to IVA monotherapy. This study aims to address this question and will also evaluate if combination of IVA and PDT may lead to a reduction in number of retreatments using an as needed anti VEGF retreatment protocol.

Another novel aspect of this protocol is the use of reduced fluence PDT (RF-PDT) as opposed to full fluence PDT used in EVEREST II trial. There have been concerns regarding full fluence-PDT, which include retinal hemorrhage post treatment, choriocapillaris non-perfusion and damage to the retinal pigment epithelium.[24–28] These concerns are particularly relevant in eyes which require repeated PDT treatments and large treatment spots.[29] RF-PDT has been proposed to have better safety profile in terms of less RPE and choriocapillaris damage,[19,20] and few studies have shown promising results in retrospective case series with comparable visual improvements and polyp regression rates.[20,29,30] A recent case control review comparing reduced and standard fluence PDT in 38 macular PCV patient showed a comparable visual gain and anatomical outcome with a polyp closure rate of 77.8% in the RF-PDT group.[30] Although the effects of RF-PDT have been studied in context of PCV, the evidence comes from small sampled cases series and this study will give us the opportunity to evaluate the effect of RF-PDT more formally in a clinical trial setting.

The third aspect of this study is to evaluate imaging biomarkers that may predict treatment outcomes in PCV. Several retrospective clinical series have reported poorer response to IVR monotherapy in eyes with thicker choroid, and better visual outcome to PDT in eyes which exhibit choroidal vascular hyperpermeability (CVH).[31,32] A recent post-hoc analysis from the EVEREST II study showed that smaller polyp area at baseline was associated with better visual outcome with IVR monotherapy.[33] Our study protocol will incorporate multimodal imaging in every study visit. We will evaluate imaging features specific to PCV, including polyp and branching vascular network size on ICGA and OCT-based features such as sharp-peaked PED and sub-RPE ring.[34,35] In addition, we will also evaluate choroidal parameters such as choroidal thickness, CVH and CVI. Variations in choroidal characteristics may reflect different predominant pathogenic process which in turn may explain the heterogeneity in treatment responses.[22,23,31,32,36–40] We will also explore the use of newer imaging modality such as OCTA which has the potential to delineate choroidal neovascularization and PCV lesion components. These parameters will be tracked non-invasively with OCTA longitudinally. Changes in lesion characteristics on OCTA, such as increase in size and branching complexity may also be early indicators of disease reactivation.[35,41–44] To date, there has been limited experience with OCTA due to various challenges like poor inter-visit registration, artefacts and segmentation inaccuracy which make quantitative analysis difficult.[45] The OCTA data collected for this study will help to fill this important gap.

In summary, this protocol will address the clinical impact of combining IVA with RF-PDT and assess novel, PCV-specific imaging biomarkers. Together these results will fill important gaps in the current understanding of the management of PCV.

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Table 1: Study visits & Procedures

Procedure/ Assessments	Screening	Baseline	WK 4	WK 8	WK 12	WK 16	WK 20	WK 24	WK 28	WK 32	WK 36	WK 40	WK 44	WK 48	WK 52 Last visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Days	-14 to 1	1	28	56	84	112	140	168	196	224	252	280	308	336	364
Visit window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Clinic Consultation (including slit lamp and dilated fundus examinations)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X														
IVI		X													X
Vital Signs	X	X			X										X
FFA	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
ICGA	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
BCVA	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
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCTA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Colour fundus Photography	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
Auto fluorescence	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
Transport allowance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IVT treatment (Eylea)		X	**Per retreatment criteria (Figure 3)**												
Verteporfin/sham RF-PDT (80 pts/ 80 pts)		X	**Per retreatment criteria (Figure 3)**												

**Screening (visit 1) and baseline (visit 2) can be done on the same day at PI/ Co-I discretion.*

[a] FFA, ICGA and colour fundus photography only to be performed if required per retreatment algorithm

Figure legends :

Figure 1: Randomized of the patients in to monotherapy or combination therapy groups

Legend : Once enrolled study participants will be randomized to 2 treatment groups using a ratio of 1:1
1) combination group: aflibercept combined with RF-PDT, IVA
2) monotherapy group: Aflibercept monotherapy with sham RF-PDT

Figure 2: Visit schedules for each randomisation group

Legend : RF-PDT/Sham PDT will be administered PRN as per protocol-specific retreatment criteria based on the presence of active polyps on ICGA . Minimum interval between two PDT treatment will be at least 12 weeks. Aflibercept administered PRN as per protocol-specific retreatment criteria. The minimum interval between two aflibercept treatment will be at least 28 days.

Figure 3: Retreatment criteria after baseline treatment

Legend : At each study visit, disease activity will be assessed by masked investigator. Presence or worsening of the disease activity is considered if 1 or more of the following criteria is present 1) Loss of BCVA >=5 letters from best achieved BCVA since baseline 2) Presence of any amount of intra-retinal fluid or any sub-retinal fluid 3) Presence of new retinal haemorrhage.
Depending on the duration since last RF-PDT treatment patient will be treated either with monotherapy Aflibercept (<12 weeks since last RF-PDT) or will undergo FFA/ICG (>12 weeks since last RF-PDT). If angiographic analysis suggests polypoidal lesion involving macula with GLD <5400 um patient will undergo Aflibercept monotherapy or Aflibercept with RF-PDT/Sham depending on the randomization groups. If no activity is noted on angiographic analysis only Aflibercept monotherapy will be administered.

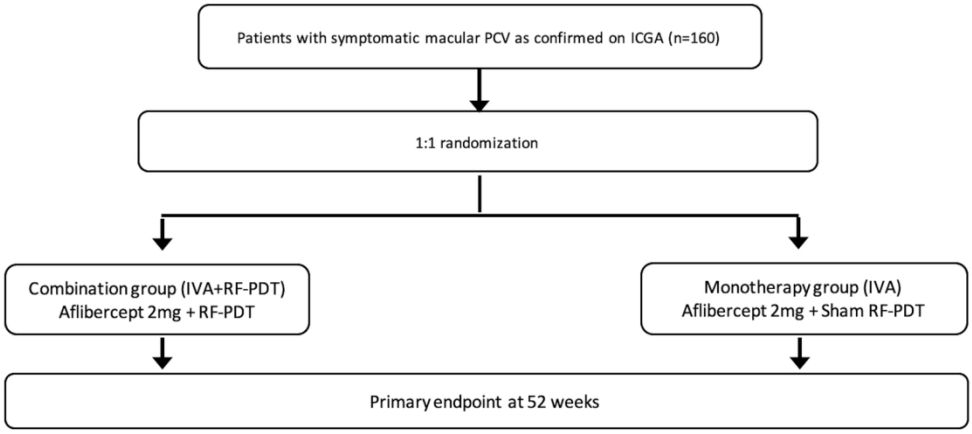
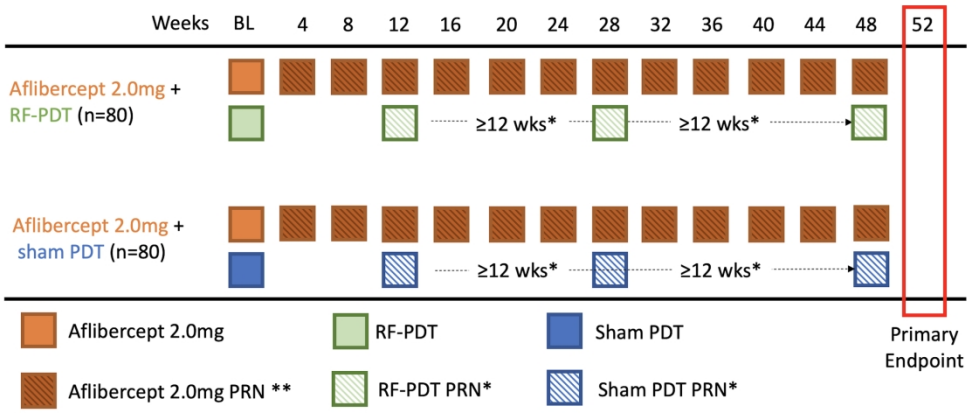


Figure 1: Randomisation of the patients in to mono-therapy or combination therapy groups. Legend : Once enrolled study participants will be randomized to 2 treatment groups using a ratio of 1:1 1) combination group: aflibercept combined with RF-PDT, IVA 2) monotherapy group: Aflibercept monotherapy with sham RF-PDT"

149x101mm (300 x 300 DPI)



*RF-PDT/Sham PDT will be administered PRN as per protocol-specific retreatment criteria based on the presence of active polyp(s) on ICGA with a minimum interval between two PDT treatments of at least 12 weeks.
**Aflibercept administered PRN as per protocol-specific retreatment criteria if there was a BCVA loss or presence of disease activity as seen on OCT. The interval between 2 aflibercept treatments must be least 28 days.

Figure 2 : Visit Schedule for each randomisation group. Legend : RF-PDT/Sham PDT will be administered PRN as per protocol-specific retreatment criteria based on the presence of active polyps on ICGA . Minimum interval between two PDT treatment will be at least 12 weeks. Aflibercept administered PRN as per protocol-specific retreatment criteria. The minimum interval between two Aflibercept treatment will be at least 28 days.

199x107mm (300 x 300 DPI)

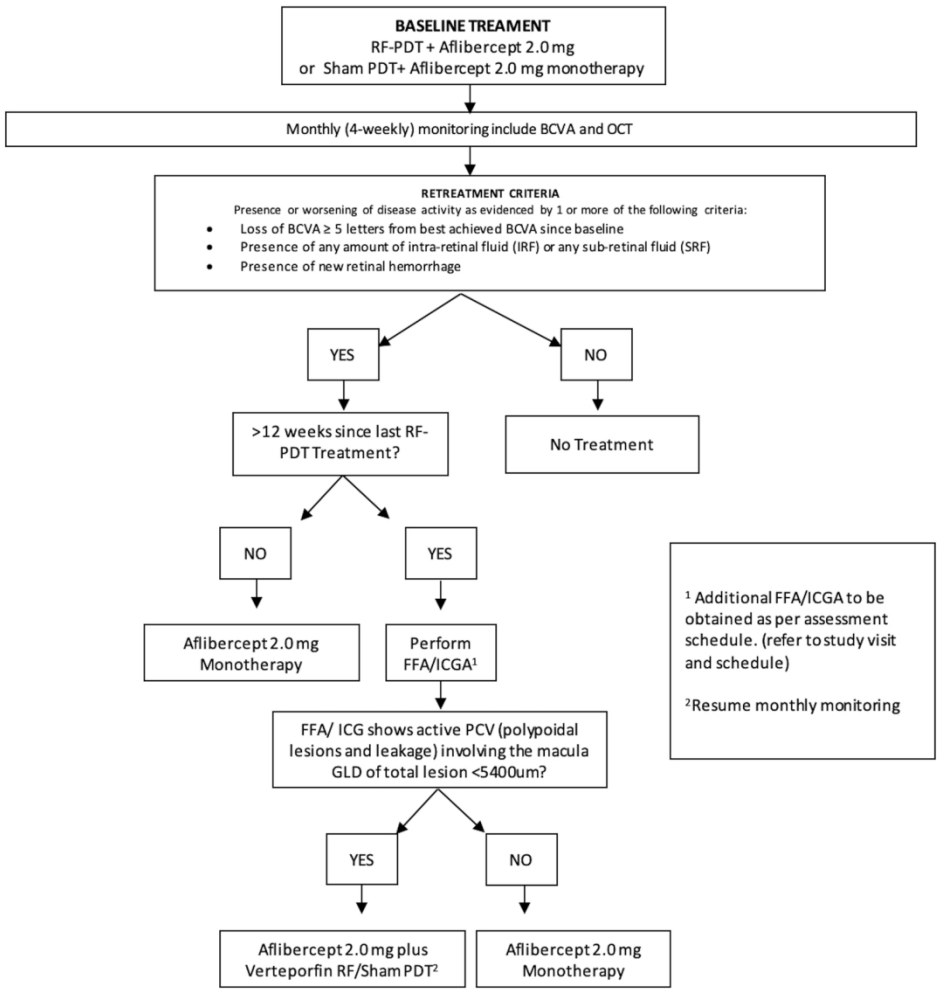


Figure 3: Retreatment criteria after baseline treatment.Legend : At each study visit, disease activity will be assessed by masked investigator. Presence or worsening of the disease activity is considered if 1 or more of the following criteria is present 1) Loss of BCVA >=5 letters from best achieved BCVA since baseline 2) Presence of any amount of intra-retinal fluid or any sub-retinal fluid 3) Presence of new retinal haemorrhage. "Depending on the duration since last RF-PDT treatment patient will be treated either with monotherapy Aflibercept (<12 weeks since last RF-PDT) or will undergo FFA/ICG (>12 weeks since last RF-PDT). If angiographic analysis suggests polypoidal lesion involving macula with GLD <5400 um patient will undergo Aflibercept monotherapy or Aflibercept with RF-PDT/Sham depending on the randomization groups. If no activity is noted on angiographic analysis only Aflibercept monotherapy will be administered."

149x165mm (300 x 300 DPI)

Supplementary Table 1. Trial registration dataset in accordance with World Health Organization (WHO)

Data category	Information[32]
Primary registry and trial identifying number	ClinicalTrials.gov Identifier: NCT03941587
Date of registration in primary registry	24/11/2020
Secondary identifying numbers	Singhealth CIRB Ref No. 2020/2857 SERI Ref. No. R1735/58/2020
Source(s) of monetary or material support	National Medical Research Council Singapore Open Fund Large Collaborative Grant (NMRCLCG17MAY013)
Primary sponsor	Singapore Eye Research Institute, Singapore National Eye Centre
Secondary sponsor(s)	Singapore Eye Research Institute, Singapore National Eye Centre
Contact for public queries	Gemmy Chui Ming Cheung, FRCO*phth* Email: gemmy.cheung.c.m@singhealth.com.sg
Contact for scientific queries	Gemmy Chui Ming Cheung, FRCO*phth* Email: gemmy.cheung.c.m@singhealth.com.sg
Public title	Comparing intravitreal Aflibercept monotherapy vs Aflibercept combined with RF-PDT in PCV treatment
Scientific title	A multi-centre, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy
Countries of recruitment	Singapore
Health condition(s) or problem(s) studied	Polypoidal Choroidal Vasculopathy
Intervention(s)	Aflibercept 2mg intravitreal injection (IVA) Monotherapy group
	Aflibercept 2mg intravitreal injection combined with RF-PDT Combination group
Key inclusion and exclusion criteria	Ages eligible for study: ≥50 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria: Treatment naïve eyes diagnosed with ICGA proven polypoidal choroidal vasculopathy; Best corrected logMAR visual acuity score between 73 to 4 letters (ie 20/32 to 20/320)
	Exclusion criteria: Known allergy to any component of the study drug. Any other ocular condition other than PCV.
Study type	Interventional
	Multi-centre Randomised, triple masked, open label, two arm, , phase 4 investigator-initiated clinical trial.
	Primary purpose: treatment
	Phase IV
Date of first enrolment	11 January 2021
Target sample size	160 subjects
Recruitment status	Recruitment started
Primary outcome(s)	compare the change in BCVA from baseline to week 52 between the combination group (IVA + RF-PDT) and the IVA monotherapy group.
Key secondary outcomes	Anatomical outcomes at week 12 and 52 between treatment groups (assessed by multimodal imaging) and Retreatment number between treatment groups

Supplementary Table 2. Polypoidal Choroidal Vasculopathy Grading Sheet (*per study visit*)

GRADING SHEET									
PDT_PCV	**DEMOGRAPHICS**				**HISTORY**				
STUDY ID	Age (yrs)	Race (Chinese/Malay/Indian)	Sex (male/female)	Laterality (right/left)	Smoking (yes/no)	HPN (yes/no)	IHD (yes/no)	DM (yes/no)	BCVA (yes/no)
PDT(SNEC)001									

PDT_PCV	**FUNDUS COLORED PHOTOS**							
STUDY ID	presence of Subretinal orange nodule (yes/no)	Presence of sub-retinal haemorrhage (yes/no)	Total lesion area (mm^2)	area of haemorrhage (mm^2)	presence of drusen (yes/no)	Soft drusen (yes/no)	Pachydrusen (yes/no)	Pseudodrusen (yes/no)
PDT(SNEC)001								

PDT_PCV	**ICGA**						**FA**			
STUDY ID **PDT_PCV**	Presence of Pachyvessels (yes/no)	choroidal vascular hyperpermeability (yes/no)	polypoidal lesions (yes/no)	branching network (yes/no)	branching network area (mm^2)	polypoidal lesions area (mm^2)	Leakage (yes/no)	Type (classic/occult)	polypoidal lesion leakage (yes/no)	BVN leakage (yes/no)
PDT(SNEC)001										

PDT_PCV	**SD - OCT**									
STUDY ID **PDT_PCV**	subretinal fluid (yes/no)	Intraretinal fluid (yes/no)	Hyper-reflective foci (yes/no)	sub-retinal hyper reflective material (yes/no)	PED > 100µm (yes/no)	Serous PED (yes/no)	Fibro-vascular PED (yes/no)	Haemorrhagic PED (yes/no)	Maximum PED width (um)	Maximum PED height (um)
PDT(SNEC)001										

PDT_PCV	**SD – OCT (continuation)**								
STUDY ID **PDT_PCV**	Foveal PED involvement (yes/no)	Double Layer (yes/no)	Notch PED (yes/no)	Sharp peaked PED (yes/no)	Sub-RPE ring lesion (yes/no)	height of ring lesion (um)	height of PED (um)	Sub foveal choroidal thickness (um)	Attenuation of choriocapillaris (yes/no)
PDT(SNEC)001									

PROTOCOL CHECKLIST			
A multi-centre, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy			
Section/item	Item No	Description	Page no
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 1
Protocol version	3	Date and version identifier	3
Funding		Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4,5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	10, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, figure 1 and 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	17

		statistical analysis plan can be found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19,20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

A multi-center, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050252.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Jun-2021
Complete List of Authors:	Vyas, Chinmayi; Singapore National Eye Centre Cheung, Chui Ming Gemmy; Singapore National Eye Centre, Medical Retina Tan, Colin; Tan Tock Seng Hospital Chee, Caroline; National University Hospital Department of Ophthalmology Wong, Kelly; Singapore Eye Research Institute Jordan-Yu, Janice; Singapore Eye Research Institute Wong, Tien; Singapore Eye Research Institute, ; Singapore National Eye Centre, Tan, Anna; Singapore National Eye Centre, Ophthalmology Fenner, Beau; Singapore National Eye Centre Sim, Shaun; Singapore National Eye Centre Teo, Kelvin Yi Chong; Singapore National Eye Centre, ; Singapore Eye Research Institute, Medical Retina
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology
Keywords:	Clinical trials < THERAPEUTICS, Medical ophthalmology < OPHTHALMOLOGY, Medical retina < OPHTHALMOLOGY

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A multi-center, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy

Chinmayi Himanshuroy Vyas [1] ,Chui Ming Gemmy Cheung [1,2] ,Colin Tan Siang Hui [2,3]
Chee Ka Lin Caroline[4], Kelly Wong Kai Li[1], Janice Marie Jordan-Yu[1]Tien Yin Wong[1,2]
Anna Cheng Sim Tan[1,2], Beau James Fenner[1], Shaun Sebastian Sim[1], Kelvin Yi Chong Teo [1,2]

1. Singapore Eye Research Institute, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751, Singapore
2. Duke-NUS Medical School, National University of Singapore, Singapore
3. National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore, Republic of Singapore
4. National University hospital, Singapore, Republic of Singapore.

Correspondence to :

Dr Kelvin Yi Chong Teo [1,2]
Consultant
Singapore Eye Research Institute, Singapore National Eye Centre
11 Third Hospital Avenue, Singapore 168751
Email : kelvin.teo.y.c@singhealth.com.sg
Telephone: + 65-6227 7266
Fax: + 65-6227 7291

Key words:
Medical retina, Clinical trials , Ophthalmology , polypoidal choroidal vasculopathy, intravitreal aflibercept, photodynamic therapy

Financial support : Financial support is provided by National Medical Research Council (NMRC) Singapore open fund large collaborative grant , NMRC/LCG/004/2018

A multi-center, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy

ABSTRACT

Purpose: To compare the efficacy and safety of intravitreal aflibercept monotherapy (IVA) vs aflibercept combined with reduced fluence PDT (IVA + RF-PDT) for the treatment of polypoidal choroidal vasculopathy (PCV)

Methods and analysis:
Multi-centred, double-masked, randomised controlled trial to compare the 2 treatment modalities. The primary outcome of the study is to compare the 52-weeks visual outcome of IVA vs IVA + RF-PDT. One hundred and sixty treatment-naïve patients with macular PCV confirmed on Indocyanine green angiography (ICGA) will be recruited from three centres in Singapore. Eligible patients will be randomized (1:1 ratio) in to one of the following groups: IVA monotherapy group- aflibercept monotherapy with sham photodynamic therapy (n=80); combination group - aflibercept with reduced fluence photodynamic therapy (n=80); Following baseline visit, all patients will be monitored at 4-weekly intervals during which disease activity will be assessed based on Best corrected visual acuity (BCVA), ophthalmic examination findings, optical coherence tomography (OCT) and angiography where indicated. Eyes that meet protocol-specified retreatment criteria will receive IVA and sham/RF-PDT according to their randomization group. Primary endpoint will be assessed as change in BCVA at week 52 from baseline. Secondary endpoints will include anatomical changes based on OCT and dye angiography as well as safety assessment. Additionally we will be collecting OCTA data prospectively for exploratory analysis.

Ethics and Dissemination:
This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the ICH E6 guidelines of Good Clinical Practice and the applicable regulatory requirements. Approval from the Singhealth centralised institutional review board has been sought prior to commencement of the study.

Strength and limitations of this study

- Multicenter randomized clinical trial with masked image grading by independent ophthalmology reading center.
- First randomized clinical trial to compare the efficacy of IVA vs IVA + RF-PDT in an Asian population.

- Baseline RF-PDT to be formally evaluated in combination with aflibercept.
- Prospective OCTA evaluation for analysis.
- Limitation: no head-on comparison between full fluence and reduced fluence PDT

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular Age related macular degeneration (nAMD) which comprises up to 50 % of exudative maculopathy in the Asian population.[1–5] Anti-vascular endothelial growth factor (anti-VEGF) therapy has been established as the standard of care for treatment of nAMD,[6–9] however the response in eyes with PCV has been less consistent.[10–13] Current best evidence for the treatment of PCV comes from two recent randomized controlled trials. The EVEREST II study reported superior visual gains and lower number of anti VEGF treatments in the intravitreal ranibizumab combined with PDT (IVR+PDT) arm compared to IVR monotherapy.[14,15] On the other hand, the PLANET study reported good visual gain (>10 letters) in the IVA monotherapy arm, and demonstrated no additional benefit of IVA with rescue PDT.[16,17] Hence both approaches are currently practised. However, there remains a gap in the evidence which is specific to aflibercept. Despite the impressive visual gain with IVA monotherapy, limited polypoidal lesion (PL) closure rate was achieved with IVA monotherapy. The lower rate of PL closure without the use of PDT in combination with anti VEGF therapy remains an area of concern clinically as unclosed PL may require regular long term treatment or increase risk of recurrence and haemorrhage.[18] There have been no randomized controlled trials to-date to evaluate whether addition of PDT to IVA would result in superior visual and/or PL closure compared to IVA monotherapy.

Here we report the methodology of a study designed to evaluate the efficacy and safety of combination IVA and PDT in patients with PCV. We hypothesize that the combination group will achieve comparable visual outcomes, higher PL closure rate with lower number of retreatments compared to IVA monotherapy. In addition, this study will use RF-PDT, which has been reported to have a better safety profile compared to full-fluence PDT.[19,20] Finally, this protocol will incorporate the analysis of novel imaging biomarkers, such as choroidal features like choroidal vascular hyperpermeability (CVH)[21,22] and choroidal vascularity index (CVI).[23] Specifically OCTA will be performed during every study visit, thus allowing for longitudinal analysis within a RCT setting.

METHODS AND ANALYSIS

Study type and study design

Multi-centred randomised controlled trial registered with Clinical trial.gov (http://clinicaltrials.gov/show/ NCT03941587). The trial registration dataset in accordance with world health organisation (WHO) is summarized in supplementary Table 1.

Protocol Number: R1735/58/2020

Protocol version : 1.1/ 02 October 2020

Study title

A multi-centre, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy

Principle investigator

Prof Gemmy Cheung Chui Ming, FRCS*Ophth*

Singapore Eye Research Institute

Study Setting:

Site 1: Singapore National Eye Centre

Contact: Prof Gemmy Cheung Chui Ming

Site 2: National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore

Contact : A/Prof Colin Tan

Site 3: National University hospital, Singapore.

Contact : A/Prof Caroline Chee

Central Reading Centre

Singapore National Eye Centre Ocular Reading Centre (SORC)

Study outcome

Primary outcome

The primary outcome of this study is to compare the change in BCVA from baseline to week 52 between the monotherapy group (IVA) and the combination group (IVA + RF-PDT)

The Primary visual outcomes are:

Final BCVA at week 52

Proportion of eyes with gain >= 5,10,15 letters at week 52

Proportion of eyes with loss >= 5,10,15 letters at week 52

Proportion of eyes with 70 or more logMAR letters

Comparison of secondary visual outcomes between groups

Secondary outcomes

The secondary anatomical outcomes are:

To compare anatomical outcomes at week 12 and 52 between treatment groups assessed by multimodal imaging

- Optical Coherence Tomography : For evidence of intraretinal or subretinal fluid, ill-defined hyper-reflective material and/or new haemorrhage [Time Frame: every month for 12 months]
- Optical Coherence Tomography-Angiograph : For evidence of intraretinal or subretinal fluid, ill-defined hyper-reflective material and/or new haemorrhage [Time Frame: every month12 months]
- Color Fundus photography : inspect anomalies associated to diseases that affect the eye, and to monitor their progression [Time Frame: baseline, month 3, month12]
- Autofluorescence Photography Retinal imaging [Time Frame: baseline, month 3, month12]
- Fundus Fluorescein Angiography for Retinal circulation [Time Frame: Baseline, month 3, month 12]
- Intra Ocular Pressure (IOP) Fluid Pressure in eye [Time Frame: Baseline, 12 months]

The secondary management outcomes are:

Total number of intravitreal injection of Aflibercept and RF-PDT treatment

Retreatment number of intravitreal injection of Aflibercept and RF-PDT treatment

Exploratory imaging analysis :

Imaging predictors CVI, CVH and sub RPE hyperreflective ring

Longitudinal changes in OCTA between the groups

Outcome definitions

Visual assessment of BCVA will be determined according to the logMAR letters in all visits

Polypoidal lesion closure will be defined as a PL disappearance as assessed by investigators and reading centre on ICGA

Efficacy assessment

All efficacy assessment include both functional and anatomical evaluation. These include comparison of following between the groups: BCVA, PL closure on ICGA, presence of intralesional or sub-lesional fluid on SD-OCT and OCTA.

Safety assessment

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

Time line

A total of 160 PCV patients recruited over approximately 16 months period (starting Feb 2021) total follow up time of 52 weeks after inclusion.

Study start date : February 1st 2021

Anticipated study end date : 31st May 2022

Sample selection

The study population will consist of a group of adults aged 50 and above with symptomatic macular PCV who are naïve to treatment in the study eye. Study participants can only have one study eye. If both eyes are eligible for the study, the eye without previous intravitreal anti-VEGF treatment will be selected. If both eyes are treatment naïve, the eye with worse BCVA should be selected as the study eye. There will be no restriction of recruitment according to the race of the patient.

Eligibility criteria

Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For potential study participants who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the potential study participant by a study investigator and study coordinator. The potential study participant will be given the informed consent form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study.

Inclusion criteria

- Male or female study participant aged >= 50 years old at the time of informed consent.
- Best corrected visual acuity early treatment diabetic retinopathy study (ETDRS) letters score of 4 to 73 letters (Snellen equivalent approximately 20/32 to 20/800) in the study eye.
- Confirmed diagnosis of symptomatic macular PCV based ICGA with activity of PCV confirmed by exudation involving the macula on OCT or FA or both.
- Presence of intra retinal or subretinal fluid/blood at the fovea as seen on OCT
- Treatment naïve
- *NO previous treatment with intravitreal anti-VEGF agents, regardless of the indication

- *NO previous thermal laser in the macular region, or verteporfin photodynamic therapy , regardless of indication
- *NO other previous treatment for nAMD, except oral supplements and traditional Chinese medicine
- Greatest Linear Dimension (GLD) of the total lesion area - Branching Vascular Network (BVN) + PL < 5400µm (~9 MPS Disc Areas) as delineated by ICGA.
- Able and Willing to provide written informed consent and comply with all scheduled visits and study procedure.

Exclusion criteria

Participant

- Medical condition that, in the opinion of the investigator, would preclude participation in the study (e.g. unstable medical status including blood pressure, cardiovascular disease, and glycaemic control).
- Participation in an investigational trial within 30 days of enrolment which involves treatment with unapproved investigational drug.
- Known allergy to any component of the study drug.
- Blood pressure > 180/110 (systolic above 180 OR diastolic above 110 on repeated measurements). If blood pressure is brought below 180/110 by anti-hypertensive treatment, individual can become eligible.
- Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 4 months prior to randomization.
- Systemic anti-VEGF or pro-VEGF treatment within four months prior to randomization or anticipated use during the study.
- Severe amblyopia (BCVA <20/100) or blind in fellow eye (BCVA < 20/800)

Study Eye

- Eye with intra retinal or subretinal fluid due to other causes than PCV
- An ocular condition is present (other than PCV) that, in the opinion of the investigator, might affect intra or sub retinal fluid or alter visual acuity during the course of the study (e.g., DME, vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.)

- Substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by more than three lines (i.e., cataract would be reducing acuity to worse than 20/40 if eye was otherwise normal).
- Any intraocular surgery within 3 months of enrolment
- Treatment with intra-vitreal corticosteroids
- History of retinal detachment or surgery for retinal detachment
- History of vitrectomy
- History of macular hole
- Evidence of vitreomacular traction that may preclude resolution of macular oedema > 4 disc areas of intra/sub retinal haemorrhage
- Aphakia
- Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis

Other Eye

- Active intraocular inflammation
- History of uveitis

Patient withdrawal

Participants may voluntarily withdraw from the study at any time. If a study participant is considering withdrawal from the study, the principal investigator should personally speak to the individual about the reasons, and every effort should be made to accommodate him or her.
Study participants who withdraw will be asked to have a final closeout visit at which the testing described for the protocol visits will be performed. Study participants who have an adverse effect attributable to a study treatment or procedure will be asked to continue in follow-up until the adverse event has resolved or stabilized.

Study assessment and visit schedule/ study procedures/ data acquisition

Screening evaluation and baseline testing

Historical Information

A history will be elicited from the potential study participant and extracted from available medical records. Data to be collected will include: age, gender, ethnicity and race, past medical history and medications being used, as well as ocular diseases, surgeries, and treatment.

Baseline Testing Procedures

- The following procedures are needed to assess eligibility and/or to serve as baseline measures for the study.
- Best-corrected Visual Acuity: BCVA will be measured using the ETDRS VA protocol following manifest refraction.
- SD-Optical Coherence Tomography : Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany and Topcon DRI OCT Triton /version 10.17.003.03, Tokyo, japan will be utilised for image acquisition. Both standard and enhanced depth imaging scans will be performed.
- OCT Angiography will be performed at baseline and each subsequent visits Topcon DRI OCT Triton /version 10.17.003.03, Tokyo, japan will be utilised to perform the OCTA.
- Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated fundus examination (within 21 days prior to randomization).
- Blood pressure measurements (Dinamap 1846 XT, Critiko Corporation, Tempa, florida , USA)
- Fundus Photography will be perfomed on TRC-50X/IMAGEnet 2000, Topcon, Tokyo, japan.
- Autofluorescence photography will be performed on the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany)
- Fundus fluorescein and Indocyanine Green angiography: FFA and ICGA will be performed (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany).

Study participants will be randomized to 2 treatment groups using a ratio of 1:1 (combination group: aflibercept combined with RF-PDT, IVA monotherapy group: Aflibercept monotherapy with sham RF-PDT)(Figure 1)

Disease characteristics of the study eye assessed by the investigator at screening (Day 1):

- Diagnosis of PCV based on ICGA
- Polypoidal lesion presence will be defined as the presence of single or multiple hyperfluorescent lesions on ICGA within the first 6 min with one or more of the following features:
- Nodular appearance on stereoscopic view of ICGA
- Hypo-fluorescent halo surrounding the focal hyperfluorescent lesion(s) on early frames
- Pulsatile filling of the lesion on video ICGA

- Presence of activity clinically as evidence by presence of haemorrhage, oedema on fundus examination.
- Presence of activity as evidence by intra retinal or sub retinal fluid on OCT

Follow-up visit schedule and examination

At each visit, study participants will be assessed based on best corrected visual acuity (BCVA), ophthalmic examination, OCT and OCT-angiograph (OCT-A). (Table 1)

In addition, colour photography, autofluorescence photography, fluorescein and indocyanine green angiography will be performed at baseline, week 12 and week 52. (Table 1)

Additional investigations at interim visits may be performed at the discretion of the investigator if there is evidence of disease activity. (Figure 2)

Qualification for retreatment with Aflibercept (Figure 3) (week 4 to week 48) will be based on signs of disease activity defined as persistent intraretinal or subretinal fluid on OCT and BCVA.

Qualification for retreatment with PDT (Figure 3) (week 4 to week 48, repeated not more frequently than 12 weeks apart) will be based on signs of persistent PL on ICGA, according to randomization group.

End of study visit

At week 52, all subjects will return for end of study visit. All subjects will be assessed based on BCVA, ophthalmic examination, FA, ICGA, colour fundus photography, Autofluorescence and OCT and OCT-A

Role of centralised reading centre

All eligibility criteria and retreatment decisions will be based on investigators assessments. All images will be sent to the SNEC ocular reading centre (SORC) at the conclusion of the clinical study for the purpose of analysis. These gradings will have no bearing on the retreatment decisions during the trial. Grading protocol is included as a supplementary table 2.

Treatment procedure

Study eyes will receive either intravitreal injection of aflibercept along with sham RF-PDT or RF- PDT depending on the assigned randomization group. (Figure 1)

When a patient's condition warrants treatment with both RF-PDT/ sham RF-PDT and Aflibercept, sham/ RF-PDT will be performed first.

Intravitreal Injection Technique

Antibiotics in the pre-, peri-, or post-injection period are not necessary but can be used at investigator discretion if such use is part of his/her usual routine.

Prior to the injection, the study eye will be anaesthetized with topical anaesthetic, followed by a povidone iodine prep of the conjunctiva. (Instil 5% povidone iodide on to the ocular surface and allow adequate time prior to injection)

Aflibercept will be withdrawn using aseptic technique through an 18-guage filter needle attached to a 1-ml syringe. The needle will be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The needle should be replaced by a sterile 30-guage needle for the intravitreal injections. The contents of the syringe should be expelled until the plunger is aligned with the line that marks 0.05ml on the syringe.

The injection will be performed using sterile technique. Investigator will use a surgical hand disinfection technique and wear sterile gloves. Periocular skin and eyelid margins and eye lashes will be cleaned with 10% povidone iodine.

Skin will be dried and drape will be applied. Investigator will insert eyelid speculum, ensuring that it is well positioned underneath the eyelids to direct the eyelashes away from the field. Callipers should be used to mark the injection site. The entry site of the needle should be 3.0- 3.5 mm from the limbus in pseudophakic patients, and 3.5-4.0 mm in phakic patients.

The conjunctiva may be displaced anteriorly using either forceps or cotton tipped applicator so that no direct route between vitreous and ocular surface remains. The needle is inserted perpendicular through sclera with the tip aimed towards the centre of the globe (to avoid any contact with the posterior lens capsule)

IOP measurement post-injection is not mandatory. While small volume injections (0.05ml) are unlikely to cause IOP rise, it should be considered in participants with ocular hypertension or glaucoma, and in all cases where participants are symptomatic for pain or reduced vision immediately following injection. Should a high intraocular pressure resulting in non-perfusion of the central retinal artery occur, indicated by no perception of light (NPL) in the treated eye, an anterior chamber paracentesis is indicated. Such decompression needs to be achieved within 3-5 minutes. Participants should be instructed to report any symptoms regarding eye pain or discomfort, increased redness of the eye, or additional blurring of vision (which may indicate endophthalmitis) to the treating ophthalmologist without delay

Delay in Giving Injections

If a scheduled injection is not given on the day of study visit, it may be administered within 7 days after the occurrence of the study visit. If it is not given by that time, it will be considered missed. If an injection is given late, the next scheduled injection should occur no sooner than 28 days after the previous injection.

Non-Study Eye Injections

If the non-study eye is going to be treated for any condition which requires treatment with an anti-VEGF agent, it may be treated at the discretion of the investigator. Treatment of the fellow- eye with aflibercept is possible.

RF-PDT/ Sham RF-PDT administration

Pre-treatment patient preparation

The verteporfin (Visudyne) / sham (5% dextrose in water solution for infusion) intravenous infusion will be administered using standard aseptic technique. The skin at the infusion site will be disinfected prior to the infusion as per local standard.

This intravenous procedure will be done using the same cannula inserted into patient for FFA/ICG procedure. There will be no additional insertion of cannula. During the infusion, the delivery syringe and intravenous line should be wrapped in aluminium to mask the identity of treatment. The active RF-PDT/ Sham RF-PDT will be performed by an unmasked investigator enrolled of the study team.

Active RF-PDT

Verteporfin will be administered according to the current Visudyne package labelling. A dosage calculated at 6mg/m2 body surface area in a 30-ml solution will be infused intravenously over a 10-minute period. Fifteen minutes after the start of the infusion (verteporfin), the study eye will be anaesthetized with topical anaesthetic and a contact lens will be used for the laser procedure. Laser light will be applied to the study eye for 83 seconds with the following parameters: Light dose (reduced fluence) 25 J/cm2, Light wavelength 689 nm

Sham RF-PDT

The sham infusion will be prepared with 5% dextrose in water solution for infusion. A 30 mL volume of this solution will be infused intravenously over a 10-minute period to mimic the verteporfin infusion. Fifteen minutes after the start of the infusion (sham solution), the study eye will be anaesthetized with topical anaesthetic and a contact lens will be used for the laser procedure. A sham laser (i.e. a true laser light will not be used) procedure that will mimic the procedure of the active RF-PDT will performed

Post treatment care

Patients who receive RF-PDT will become temporarily photosensitive after the infusion. All patients who receive verteporfin RF-PDT/ sham RF-PDT will be instructed to avoid direct sunlight for 48 hours.

Treatment Regimen Adjustments

If the study eye develops a treatment-related adverse event at any time during the study, treatment dose may be temporarily held and the reason for dose holding will be recorded in the CRF.

The treatment regimen will be adjusted based on the following criteria:

• Intraocular inflammation: may hold dose at the investigator's discretion, eg, if intraocular inflammation is >= 2+ in the study eye. Treatment may resume when the inflammation has resolved.

• IOP: hold dose if IOP is >= 30 mm Hg in the study eye. Treatment may resume when IOP is <= 30 mm Hg, either spontaneously or by treatment, as determined by evaluating physician.

• New retinal break or retinal detachment: hold dose for the study eye. Treatment may resume after the retinal break/detachment had been successfully treated.

• Ocular and/or periocular infection: hold dose until the infection is resolved in both eyes.

The investigator may hold or discontinue study treatment for other safety reasons at his/her discretion.

Randomization and blinding

Study participants will be randomized to 2 treatment groups using a ratio of 1:1(combination group: aflibercept combined with RF-PDT, IVA monotherapy group: Aflibercept monotherapy with sham RF-PDT)(Figure 1) and randomization will be performed using a blocked randomization method. Each site will be randomized to a 1:1 ratio for each study treatment arm.

The site at the Singapore national eye centre (SNEC) will be randomized in blocks of 20 and the remaining 18 participants will be randomized in blocks of 9. For the Tan Tock Seng Hospital (TTSH) site, 30 participants will be randomized in blocks of 10. For the National University hospital (NUH) site, 32 participants will be randomized in block of 20, with the remaining 12 participants randomized in blocks of 6.

Blinding : Initial assessment and recruitment of the patient will be done by the masked Co- investigator and Masked Research co-ordinators. The treatment procedure will be done by the unmasked co-Investigators. Both participants and masked team will be masked to treatment received.

Unblinding will be permissible only in circumstances involving SAE.

Study completion

All participants that have completed 52 weeks of treatment are considered to have completed the study successfully.

Treatment schedule

Treatment randomization is summarized in Figure 1.

All participant with macular PCV will be assessed at baseline and randomized to each study treatment arm (combination group: aflibercept combined with RF-PDT, IVA monotherapy group: Aflibercept monotherapy with sham RF-PDT)

At the baseline visit, depending on the randomization the combination group will receive IVA and RF-PDT while the monotherapy group with receive IVA + sham PDT.

After baseline visit, patients will be monitored at 4 weekly interval between week 8 and 48

At each study visit, disease activity will be assessed by masked investigator. If disease activity is present according to the prespecified treatment protocols (figure 3), patients will be treated according to randomisation arm. All clinical evaluations during study visits will be carried out by the masked investigator while treatment administration will be undertaken by the unmasked investigator.

Study medication

Aflibercept (EYLEA): study eyes will receive a dose of 2mg in 0.05 ml of aflibercept

Verteporfin RF-PDT/ Sham RF-PDT: Verteporfin will be administered according to the current Visudyne package labelling. A dosage calculated at 6mg/m2 body surface area in a 30-ml solution will be infused intravenously over a 10-minute period. Fifteen minutes after the start of the infusion (verteporfin), the study eye will be anaesthetized with topical anaesthetic and a contact lens will be used for the laser procedure. Laser light is applied to the study eye for 83 seconds with the parameters: Light dose (reduced fluence) 25 J/cm2, Light wavelength 689 nm

Dosage form, packaging and labelling

Aflibercept (EYLEA) is solution for injection, clear, colourless to pale yellow, iso-osmotic solution, pH6.2. following intravitreal injection of 2 mg per eye of the mean Cmax of free aflibercept in the plasma was noted to be 0.02mcg/ mL(range :0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free aflibercept plasma concertation was undetectable two weeks post dosing.

Visudyne vial contains 15mg of verteporfin. After constitution, 1 mL contains 2mg of verteporfin. 5mL of reconstituted solution contains 15mg of verteporfin.

Sham RF-PDT consists of dextrose 5% solution followed by light application RF-PDT.

The sham infusion will be prepared with 5% dextrose in water solution for infusion. A 30 mL volume of this solution is infused intravenously over a 10 minute period to mimic the verteporfin infusion.

Storage and drug accountability

Aflibercept (EYLEA) will be stored in a refrigerator at 2°C to 8°C. It will be stored securely in the SERI Pharmacy, SNEC building. It will be monitored by a 24-hour Temperature monitoring System (TMS) and report will be generated on a bio-weekly basis. Alarms to any excursion will be triggered and the designated staff will be informed.

Visudyne will be stored in the original package in order to protect from light, at a room temperature not above 25°C. It will be stored securely in the SERI Pharmacy cabinet with restricted access.

The label on each Aflibercept/ Visudyne/ Dextrose 5% will include short study title, the name and country of origin of the manufacturer, batch number, trial number, expiry date, storage conditions, emergency contacts, subject no/ initials, date of dispensed, visit/ week and the words "For Clinical Trial Use Only".

Concomitant treatment

Any concomitant medications used by the subject from the date of enrolment until the end of the study except for routine medications given for ocular procedures require by the protocol, i.e fluoresceine, indocyanine, dilating drops and topical anaesthetics should be recorded as concomitant medications including the start and stop dates and indications.

Other non Anti VEGF therapy or intravitreal corticosteroids in the study eye are not allowed.

If the fellow-eye needs treatment for wet AMD (including PCV) , subjects can be treated in accordance to standard of care and continue in the study. All medications (prescription and over the counter), vitamin and mineral supplements, and / or herbs taken by the participant will be documented.

Study completion and poststudy treatment

Last visit will occur at week 52 (+/- 7 days)

No special procedures will be carried out in addition to that stated in the schedule. Participants will not receive any treatment at the study completion visit.

Study participants will continue their routine follow – up with their regular physicians upon completion of the final study. There will be no post study visits planned.

Safety assessment

Parameters

Safety parameters will include assessment of IOP,AE(adverse events) and serious adverse event.

SAE and serious adverse reaction (SAR), are defined as any Untoward medical occurrence or effect that , at any dose result in death, is life threatening, requires hospitalisation or prolongation of existing

hospitalisation, results in persistent or significant disability or incapacity or is an important medical event.

Adverse event

Adverse events are defined as the following and 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 pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study and 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.

Reporting and follow-up

Reporting of adverse events involves the Principal Investigator submitting to Centralised Institutional Review Board (CIRB) the SAE Reporting Form to CIRB within the stipulated timeframe. The Principal Investigator is responsible for informing the institution representative, the chairman medical board (when required by the institution for local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- Local unexpected SAE resulting in death that are related events should be reported immediately - within 24 hours of the Principal Investigator becoming aware of the event.
- Local unexpected, life-threatening SAE that are related events should be reported as soon as possible but no later than 7 calendar days after the Principal Investigator is aware of the event, followed by a full report within 8 additional calendar days.
- Local unexpected, not life-threatening SAE that are related events, should be reported no later than 15 calendar days after the Principal Investigator is aware of the event.
- An increase in the rate of occurrence of Local expected SAE that are related events, which is judged to be clinically important, should be reported within 15 calendar days after the Principal Investigator is aware of the event.
- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and related should be reported not later than 30 calendar days after the principal investigator is aware of the event. The review will be done on monthly basis for standard aggregate adverse event (AE) safety data report

The following standard aggregate AE safety data reports will be reviewed:

- Number and percentage of enrolled subjects reporting adverse events (AEs) by body system (i.e., primary system organ class) and preferred term in descending frequency order.
- Serious adverse events (SAE) (treatment or procedure related and non-related)- cumulative
- All AEs

The following reports of additional study – specific data will be reviewed

1)Targeted adverse events

- Intraocular inflammation/infection including AC inflammation, uveitis, vitritis, iritis, iridocyclitis, choroiditis, retinal vasculitis and endophthalmitis
- Visual acuity reduced
- Intraocular pressure increase
- Retinal tear
- Retinal detachment
- Vitreous haemorrhage
- Retinal haemorrhage
- Macular scar
- Systemic VEGF inhibition

2) Biomicroscopy/ indirect ophthalmoscopy (by visit per subject)
≥ 2 grade increase in each separate parameter (Corneal edema, Conjunctival hyperemia, Anterior chamber cells, Anterior chamber flare, Keratic precipitates, Vitreous cells, Vitreous flare/haze) and documented changes in vitreous, optic disc and retina from baseline.

3) BCVA ≥ 15 letters decrease from baseline at any visit (by visit per subject)

Data governance and safety

A Data and Safety Monitoring Committee will approve the protocol, template informed consent form, and substantive amendments and provide independent monitoring of adverse events. Cumulative adverse event data are semi-annually tabulated for review by the DSMC. Following each DSMC data review, a summary will be made available for submission to Institutional Review Board. A list of specific adverse events to be reported to the DSMC expeditiously will be compiled and included as part of the DSMC Standard Operating Procedures

Data analysis

Determination of sample size

Assuming a drop out 10% , 80 subjects per treatment arm will be adequate to demonstrate non-inferiority of the combination arm (within a 5-letter non-inferiority margin, alpha=0.025 (one sided), power=0.8), assuming BCVA gain of 11.5 letters in the combination arm vs 10.7 letters in the monotherapy. Furthermore, we will be able to demonstrate superiority of combination over monotherapy arms with a 3-letter superiority difference assuming a BCVA gain of 13.7 letters in the combination arm vs 10.7 letters in the monotherapy (alpha=0.025 (one sided), power=0.8) and assuming a drop out 10%). Furthermore, this same sample size will detect a difference in number of injections of 2 based on reducing from 7.3 in the monotherapy arm vs 5.2 in the combination arm with >99% power (injection numbers are based on EVEREST II study data).

Statistical Methods

For statistical purposes, baseline will be defined as the last available non-missing value collected just prior to the start of treatment in the study eye. For patients with screening assessments but who do not enter the treatment period, data will only be listed. For all patients only one eye will be considered as the study eye, and only for this eye efficacy analysis will be performed. Unless otherwise specified, all statistical tests will be two-sided with a 0.05 level of significance, and all confidence intervals will be two-sided with 95% confidence level.

Categorical variables will be presented as the number and percentage of patients in each category. Continuous variables will be summarized using descriptive statistics (e.g. n, mean, standard deviation, median, minimum, and maximum). Descriptive statistics will be provided for patient demographics and all baseline characteristics. Relevant medical history and current medical conditions will be tabulated by system organ class and preferred term of the MedDRA dictionary. Separate tables will be provided for ocular and non-ocular histories and conditions. Full analysis set (FAS) comprises all patients to whom treatment regimen has been assigned.

Intent-to-treat (ITT): patients will be analysed according to the treatment regimen they are assigned to at randomization. No data will be excluded from the FAS analyses because of protocol deviation. All efficacy evaluations will be carried out on the FAS.

Per protocol Set (PPS) will consist of all patients in the FAS who followed the treatment regimen as randomized and completed Week 24 without clinically significant protocol deviations.

Primary efficacy evaluation will be carried out on both the FAS and the PP set. The primary variable is the change in BCVA at Week 52 compared to baseline. The primary analysis will be performed on the FAS using the LOCF approach for imputing missing data. The statistical testing will be carried out using paired t-test. The analysis will be repeated for the PP set using the same model.

Analysis of secondary endpoints will focus on the study eye only and will be based on the FAS. At all the time points assessed, each efficacy variable will be presented graphically and descriptive statistics

provided based on absolute values and changes from baseline. For continuous and ordered categorical variables, changes from baseline will be compared between treatment groups using ANOVA.ANCOVA models/ t-test and stratified/unstratified Cochran-mantel-Hansel tests. Stratification will follow the approach described for the primary analysis as applicable. Logistic regression will be used for analyses of binary endpoints.

Primary and secondary variables

Primary variables

Change in BCVA baseline to week 52 : BCVA at week 52 minus BCVA at baseline, Loss of ≥ 5 letters from Best Corrected Visual Acuity since baseline

Secondary variables

- Final BCVA at week 52
- Proportion of eyes with gain >= 5,10,15 logMAR letters at week 52
- Proportion of eyes with loss >= 5,10,15 logMAR letters at week 52
- Proportion of eyes with 70 or more logMAR letters at week 52
- Proportion of eyes with PL closure at week 12 and 52 assessed by ICGA
- Proportion of eyes with Presence of intraretinal and sub-retinal fluid at week 12 and 52 as evidence by OCT
- Mean number of intravitreal injections of aflibercept and RF-PDT
- Frequency and severity of ocular and non-ocular adverse events over 52 weeks
- Evaluate the influence of anatomical Imaging predictors such as CVI, CVH and sub RPE hyperreflective ring at week 12 and 52 between treatment groups (assessed by multimodal imaging).
- Longitudinal changes in OCTA between the groups

Reporting study deviations from the planned statical analysis

Deviations from the planned statical analysis will be reported in the final study report

Safety analysis

Only treatment-emergent AEs will be considered. The number and percentage of subjects reporting AEs will be reported

Access to source data/documents

Case report files (CRFs) will be reviewed with the investigators study team before study initiation and baseline visit. During the study , the following parameters will be ascertained
1)completeness of the records 2) accuracy of entries 3) adherence to the protocol and good clinical practices 4) progress of the enrolment 5) storage, dispensing and accounting of the study medications

source documentations will be available for monitoring and audit for compliance with clinical protocol. Monitoring standards require verification of presence of informed consent, adherence to the inclusion /exclusion criteria , report of SAEs and recording of data that will be used for efficacy and safety variables. Source documentation should not contain any participant identifiers .

Ethics and dissemination

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

Regulatory and ethical compliance

The investigator(s) and institution(s) will permit and facilitate all study related monitoring audit(s) and regulatory review(s) and inspection(s), providing direct access to source data/ documents.

Informed consent procedures

Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For potential study participants who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the potential study participant by a study investigator.

The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study.

Responsibilities of the investigator

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement

Data handling and record keeping

Research data will be anonymized as soon as possible and both identification key and the de-identified data will store in separate folders in the institution access-controlled shared folders. Case files will be kept under lock and key, with restricted access to the key, as defined within the study delegation log. The study data will be stored for at least 15 years and then destroyed or deleted.

Patient and public involvement

Patients are not invited to comment on the study design and are not consulted to develop patient relevant outcomes or interpret results. Patients are not invited to contribute to the writing or editing of this document for reliability or accuracy.

Financing and insurance

Financial support is provided by national medical research council Singapore open fund large collaborative grant and covered under national clinical trial insurance policy.

Publication policy

On study completion and finalisation of the study report the results of this trail will be submitted for publication in accordance to institutional publication policy of Singapore Eye Research Institute / Singapore National Eye Centre

Protocol adherence

Investigators ascertain that they will apply due diligence to adhere to the study protocol and avoid protocol deviations

Protocol amendments

Change and addition to the protocol can only be made in written protocol amendment that must be approved by the CIRB. Amendments will required informed consent forms and/or other study- related material revision. If with informed consent form revision all subject enrolled in the study must sign the approved, revised informed consent form.

DISCUSSION

Our study aims to ascertain the effectiveness of Aflibercept monotherapy or in combination with RF-PDT using a PRN treatment regimen. Prior reports such as The EVEREST II and PLANET studies have demonstrated that both anti-VEGF monotherapy and combination of anti-VEGF with PDT can achieve

positive visual outcomes in eyes with PCV.[14–17] In the EVEREST II study, the combination (IVR +PDT) group achieved superior visual gain compared to the monotherapy (IVR) group (+7 vs +5 letters gain) with on average 2 less IVR injections over 1 year.[14,15] In the PLANET study, both monotherapy arm (IVA) and IVA with rescue PDT arm achieved >10 letters improvement at 1 year and no benefit from rescue PDT was demonstrated.[16,17] Almost 78% of eyes achieved a fluid free retina after the initial three loading doses of IVA.

Our study also aims to assess the importance of polypoidal lesion (PL) closure as a secondary endpoint for our study. PL closure is thought to be important for reducing the risk of long-term recurrence and massive sub-macular hemorrhage [18]. We have defined PL closure as no PL detected on ICGA alone which will be determined by our reading center (SORC). Both the PLANET and EVEREST II studies have evaluated a similar anatomical end point defined as complete polypoidal lesion regression in the EVEREST II study and complete closure rates of PL in the Planet study. Both these anatomical endpoints are are defined as no PL lesion seen on ICGA. The EVEREST II study showed a significantly higher polyp regression in the combination arm compared to IVR monotherapy (69.7% vs 33.8%).[14] The proportion of patients with complete closure rate reported in the PLANET study was 38.9% for the IVA monotherapy and 44.8% for IVA with rescue PDT arm at week 52.[16]

Two year results of Planet reported that the favourable visual outcome of IVI monotherapy at year one was also maintained at second year and <20% of the patients needed rescue PDT . However patients requiring rescue PDT had significantly lower visual acuity gain. Unfortunately till today there are only few studies evaluating the specific imaging or clinical characteristics to identify this group of poor responders and the role and timing of PDT and whether combination of IVA with PDT at baseline may achieve favourable visual and anatomical outcomes compared to IVA monotherapy. This study aims to address this question and will also evaluate if combination of IVA and PDT may lead to a reduction in number of retreatments using an as needed anti VEGF retreatment protocol.

Another novel aspect of this protocol is the use of reduced fluence PDT (RF-PDT) as opposed to full fluence PDT used in EVEREST II trial. There have been concerns regarding full fluence-PDT, which include retinal hemorrhage post treatment, choriocapillaris non-perfusion and damage to the retinal pigment epithelium.[24–28] These concerns are particularly relevant in eyes which require repeated PDT treatments and large treatment spots.[29] RF-PDT has been proposed to have better safety profile in terms of less RPE and choriocapillaris damage,[19,20] and few studies have shown promising results in retrospective case series with comparable visual improvements and polyp regression rates.[20,29,30] A recent case control review comparing reduced and standard fluence PDT in 38 macular PCV patient showed a comparable visual gain and anatomical outcome with a polyp closure rate of 77.8% in the RF-PDT group.[30] Although the effects of RF-PDT have been studied in context of PCV, the evidence

comes from small sampled cases series and this study will give us the opportunity to evaluate the effect of RF-PDT more formally in a clinical trial setting.

Non- monthly treatment regimen as defined by disease activity is currently practiced by most physicians in the treatment of nAMD. These include mainly the treat and extend (TNE) regimen and pro re nata (PRN) regimen. With continued focus on reducing the treatment burden and to improve the cost effectiveness for PCV we wish to closely examine a PRN IVA regimen in this study. We believe that a PRN dosing regimen after an initial IVA injection at baseline with close monthly follow up will allow us to identify the disease activity biomarkers that can predict the minimal effective IVA retreatment for PCV. Our proposed study is similar to the recently published clinical trial protocol for the Atlantic study that outlines a clinical trial aiming to evaluate the safety and efficacy of Aflibercept in PCV either alone or in combination with PDT in the Caucasian population. [31] However, unlike our study this clinical trial aims to evaluate baseline full fluence PDT and TNE regimen for retreatment.

The third aspect of this study is to evaluate imaging biomarkers that may predict treatment outcomes in PCV. Several retrospective clinical series have reported poorer response to IVR monotherapy in eyes with thicker choroid, and better visual outcome to PDT in eyes which exhibit choroidal vascular hyperpermeability (CVH).[32,33] A recent post-hoc analysis from the EVEREST II study showed that smaller polyp area at baseline was associated with better visual outcome with IVR monotherapy.[34] Our study protocol will incorporate multimodal imaging in every study visit. We will evaluate imaging features specific to PCV, including polypoidal lesion and branching vascular network size on ICGA and OCT-based features such as sharp-peaked PED and sub-RPE ring.[35,36] In addition, we will also evaluate choroidal parameters such as choroidal thickness, CVH and CVI. Variations in choroidal characteristics may reflect different predominant pathogenic process which in turn may explain the heterogeneity in treatment responses.[22,23,32,33,37–41] We will also explore the use of newer imaging modality such as OCTA which has the potential to delineate choroidal neovascularization and PCV lesion components. These parameters will be tracked non-invasively with OCTA longitudinally. Changes in lesion characteristics on OCTA, such as increase in size and branching complexity may also be early indicators of disease reactivation.[36,42–45] To date, there has been limited experience with OCTA due to various challenges like poor inter-visit registration, artefacts and segmentation inaccuracy which make quantitative analysis difficult.[46] The OCTA data collected for this study will help to fill this important gap.

In summary, this protocol will address the clinical impact of combining IVA with RF-PDT and assess novel, PCV-specific imaging biomarkers. Together these results will fill important gaps in the current understanding of the management of PCV.

Conflicts of interest

The authors declare that they have no known competing financial interests, conflict of interest or personal relationships that could have appeared to influence the design , execution and reporting of this study.

Roles and responsibilities : contributor ship

Study conception and design : GCMG and KYCT conceived the study. GCMG is the grant holder GCMG, KYCT, CT , CC initiated the study design and helped with implementation. JJ, CHV and KYCT provided statistical expertise in clinical trial design

IRB approval : GCMG, KW, KYCT

Manuscript drafting : CHV, GCMG, KYCT

Critical revision and refinement : WTY, ACST, BF, SS

All authors contributed to refinement of the study protocol and approved the final manuscript.

Roles and responsibilities of sponsor and funder

This funding source had no role in the design and conduct of this study and will not have any role during its execution, analysis , interpretation of data or decision to submit results

Trial sponsor: Singapore Eye Research Institute / Singapore National Eye Centre

Reference : SERI Ref. No. R1735/58/2020

Address :11 Third Hospital Avenue, Singapore 168751, Singapore

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Table 1: Study visits & Procedures

Procedure/ Assessments	Screening	Baseline	WK 4	WK 8	WK 12	WK 16	WK 20	WK 24	WK 28	WK 32	WK 36	WK 40	WK 44	WK 48	WK 52 Last visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Days	-14 to 1	1	28	56	84	112	140	168	196	224	252	280	308	336	364
Visit window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Clinic Consultation (including slit lamp and dilated fundus examinations)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X														
IVI		X													X
Vital Signs	X	X			X										X
FFA	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
ICGA	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
BCVA	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
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCTA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Colour fundus Photography	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
Auto fluorescence	X				X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X
Transport allowance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IVT treatment (Eylea)		X	**Per retreatment criteria (Figure 3)**												
Verteporfin/sham RF-PDT (80 pts/ 80 pts)		X	**Per retreatment criteria (Figure 3)**												

**Screening (visit 1) and baseline (visit 2) can be done on the same day at PI/ Co-I discretion.*

[a] FFA, ICGA and colour fundus photography only to be performed if required per retreatment algorithm

Figure legends :

Figure 1: Randomized of the patients in to monotherapy or combination therapy groups

Legend : Once enrolled study participants will be randomized to 2 treatment groups using a ratio of 1:1
1) combination group: aflibercept combined with RF-PDT, IVA
2) monotherapy group: Aflibercept monotherapy with sham RF-PDT

Figure 2: Visit schedules for each randomisation group

Legend : RF-PDT/Sham PDT will be administered PRN as per protocol-specific retreatment criteria based on the presence of active polyps on ICGA . Minimum interval between two PDT treatment will be at least 12 weeks. Aflibercept administered PRN as per protocol-specific retreatment criteria. The minimum interval between two aflibercept treatment will be at least 28 days.

Figure 3: Retreatment criteria after baseline treatment

Legend : At each study visit, disease activity will be assessed by masked investigator. Presence or worsening of the disease activity is considered if 1 or more of the following criteria is present 1) Loss of BCVA >=5 letters from best achieved BCVA since baseline 2) Presence of any amount of intra-retinal fluid or any sub-retinal fluid 3) Presence of new retinal haemorrhage.
Depending on the duration since last RF-PDT treatment patient will be treated either with monotherapy Aflibercept (<12 weeks since last RF-PDT) or will undergo FFA/ICG (>12 weeks since last RF-PDT). If angiographic analysis suggests polypoidal lesion involving macula with GLD <5400 um patient will undergo Aflibercept monotherapy or Aflibercept with RF-PDT/Sham depending on the randomization groups. If no activity is noted on angiographic analysis only Aflibercept monotherapy will be administered.

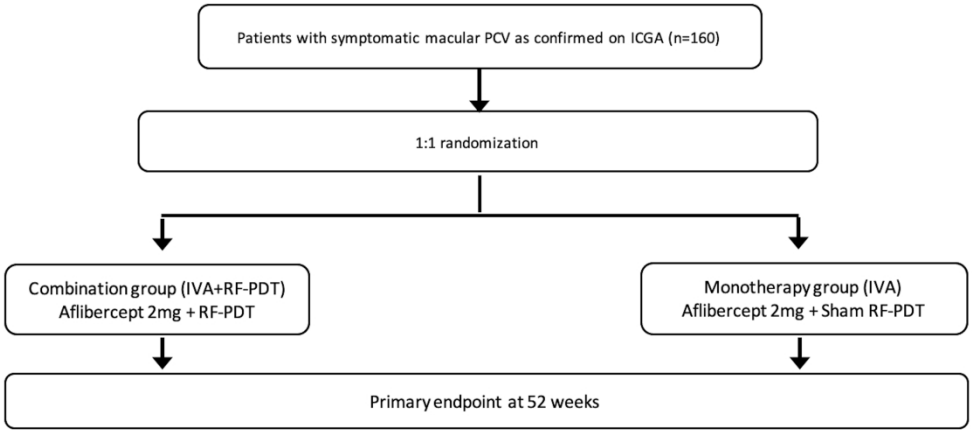
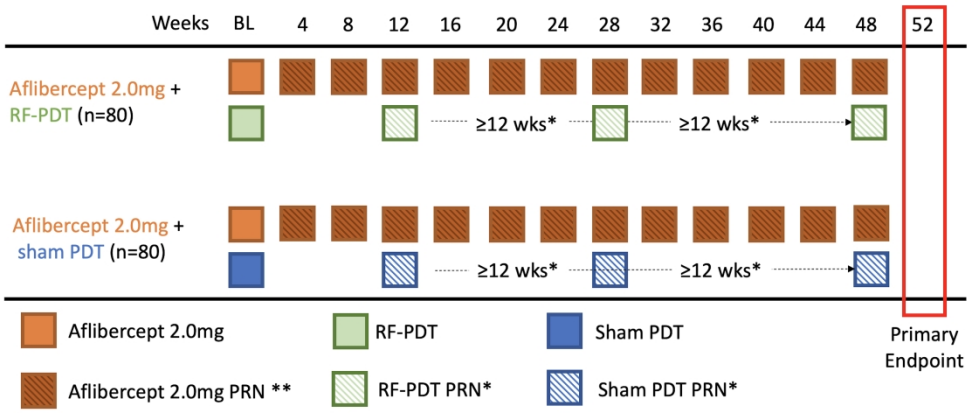


Figure 1: Randomisation of the patients in to mono-therapy or combination therapy groups. Legend : Once enrolled study participants will be randomized to 2 treatment groups using a ratio of 1:1 1) combination group: aflibercept combined with RF-PDT, IVA 2) monotherapy group: Aflibercept monotherapy with sham RF-PDT"

149x101mm (600 x 600 DPI)



*RF-PDT/Sham PDT will be administered PRN as per protocol-specific retreatment criteria based on the presence of active polyp(s) on ICGA with a minimum interval between two PDT treatments of at least 12 weeks.
**Aflibercept administered PRN as per protocol-specific retreatment criteria if there was a BCVA loss or presence of disease activity as seen on OCT. The interval between 2 aflibercept treatments must be least 28 days.

Figure 2 : Visit Schedule for each randomisation group. Legend : RF-PDT/Sham PDT will be administered PRN as per protocol-specific retreatment criteria based on the presence of active polyps on ICGA . Minimum interval between two PDT treatment will be at least 12 weeks. Aflibercept administered PRN as per protocol-specific retreatment criteria. The minimum interval between two Aflibercept treatment will be at least 28 days.

199x107mm (600 x 600 DPI)

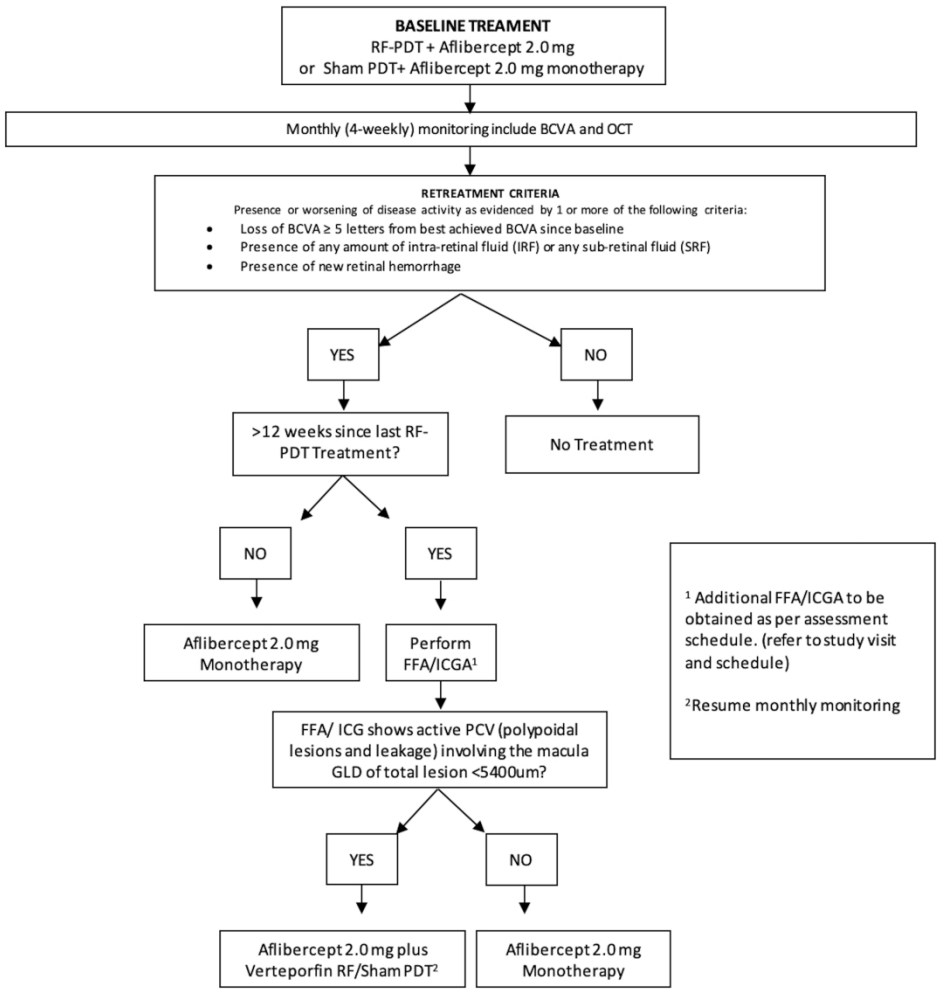


Figure 3: Retreatment criteria after baseline treatment.Legend : At each study visit, disease activity will be assessed by masked investigator. Presence or worsening of the disease activity is considered if 1 or more of the following criteria is present 1) Loss of BCVA >=5 letters from best achieved BCVA since baseline 2) Presence of any amount of intra-retinal fluid or any sub-retinal fluid 3) Presence of new retinal haemorrhage. "Depending on the duration since last RF-PDT treatment patient will be treated either with monotherapy Aflibercept (<12 weeks since last RF-PDT) or will undergo FFA/ICG (>12 weeks since last RF-PDT). If angiographic analysis suggests polypoidal lesion involving macula with GLD <5400 um patient will undergo Aflibercept monotherapy or Aflibercept with RF-PDT/Sham depending on the randomization groups. If no activity is noted on angiographic analysis only Aflibercept monotherapy will be administered."

149x165mm (600 x 600 DPI)

Supplementary Table 1. Trial registration dataset in accordance with World Health Organization (WHO)

Data category	Information[32]
Primary registry and trial identifying number	ClinicalTrials.gov Identifier: NCT03941587
Date of registration in primary registry	24/11/2020
Secondary identifying numbers	Singhealth CIRB Ref No. 2020/2857 SERI Ref. No. R1735/58/2020
Source(s) of monetary or material support	National Medical Research Council Singapore Open Fund Large Collaborative Grant (NMRCLCG17MAY013)
Primary sponsor	Singapore Eye Research Institute, Singapore National Eye Centre
Secondary sponsor(s)	Singapore Eye Research Institute, Singapore National Eye Centre
Contact for public queries	Gemmy Chui Ming Cheung, FRCO*phth* Email: gemmy.cheung.c.m@singhealth.com.sg
Contact for scientific queries	Gemmy Chui Ming Cheung, FRCO*phth* Email: gemmy.cheung.c.m@singhealth.com.sg
Public title	Comparing intravitreal Aflibercept monotherapy vs Aflibercept combined with RF-PDT in PCV treatment
Scientific title	A multi-centre, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy
Countries of recruitment	Singapore
Health condition(s) or problem(s) studied	Polypoidal Choroidal Vasculopathy
Intervention(s)	Aflibercept 2mg intravitreal injection (IVA) Monotherapy group
	Aflibercept 2mg intravitreal injection combined with RF-PDT Combination group
Key inclusion and exclusion criteria	Ages eligible for study: ≥50 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria: Treatment naïve eyes diagnosed with ICGA proven polypoidal choroidal vasculopathy; Best corrected logMAR visual acuity score between 73 to 4 letters (ie 20/32 to 20/320)
	Exclusion criteria: Known allergy to any component of the study drug. Any other ocular condition other than PCV.
Study type	Interventional
	Multi-centre Randomised, triple masked, open label, two arm, , phase 4 investigator-initiated clinical trial.
	Primary purpose: treatment
	Phase IV
Date of first enrolment	11 January 2021
Target sample size	160 subjects
Recruitment status	Recruitment started
Primary outcome(s)	compare the change in BCVA from baseline to week 52 between the combination group (IVA + RF-PDT) and the IVA monotherapy group.
Key secondary outcomes	Anatomical outcomes at week 12 and 52 between treatment groups (assessed by multimodal imaging) and Retreatment number between treatment groups

Supplementary Table 2. Polypoidal Choroidal Vasculopathy Grading Sheet (*per study visit*)

GRADING SHEET									
PDT_PCV	**DEMOGRAPHICS**				**HISTORY**				
STUDY ID	Age (yrs)	Race (Chinese/Malay/Indian)	Sex (male/female)	Laterality (right/left)	Smoking (yes/no)	HPN (yes/no)	IHD (yes/no)	DM (yes/no)	BCVA (yes/no)
PDT(SNEC)001									

PDT_PCV	**FUNDUS COLORED PHOTOS**							
STUDY ID	presence of Subretinal orange nodule (yes/no)	Presence of sub-retinal haemorrhage (yes/no)	Total lesion area (mm^2)	area of haemorrhage (mm^2)	presence of drusen (yes/no)	Soft drusen (yes/no)	Pachydrusen (yes/no)	Pseudodrusen (yes/no)
PDT(SNEC)001								

PDT_PCV	**ICGA**						**FA**			
STUDY ID **PDT_PCV**	Presence of Pachyvessels (yes/no)	choroidal vascular hyperpermeability (yes/no)	polypoidal lesions (yes/no)	branching network (yes/no)	branching network area (mm^2)	polypoidal lesions area (mm^2)	Leakage (yes/no)	Type (classic/occult)	polypoidal lesion leakage (yes/no)	BVN leakage (yes/no)
PDT(SNEC)001										

PDT_PCV	**SD - OCT**									
STUDY ID **PDT_PCV**	subretinal fluid (yes/no)	Intraretinal fluid (yes/no)	Hyper-reflective foci (yes/no)	sub-retinal hyper reflective material (yes/no)	PED > 100µm (yes/no)	Serous PED (yes/no)	Fibro-vascular PED (yes/no)	Haemorrhagic PED (yes/no)	Maximum PED width (um)	Maximum PED height (um)
PDT(SNEC)001										

PDT_PCV	**SD – OCT (continuation)**								
STUDY ID **PDT_PCV**	Foveal PED involvement (yes/no)	Double Layer (yes/no)	Notch PED (yes/no)	Sharp peaked PED (yes/no)	Sub-RPE ring lesion (yes/no)	height of ring lesion (um)	height of PED (um)	Sub foveal choroidal thickness (um)	Attenuation of choriocapillaris (yes/no)
PDT(SNEC)001									

PROTOCOL CHECKLIST			
A multi-centre, randomized clinical trial comparing intravitreal aflibercept monotherapy vs aflibercept combined with reduced fluence photodynamic therapy (RF-PDT) for the treatment of polypoidal choroidal vasculopathy			
Section/item	Item No	Description	Page no
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary table 1
Protocol version	3	Date and version identifier	3
Funding		Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4,5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	10, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, figure 1 and 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	17

		statistical analysis plan can be found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19,20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A