STUDY PROTOCOL

PROTOCOL TITLE:
An open label-study to compare the efficacy of Aflibercept monotherapy for Polypoidal Choroidal Vasculopathy using a modified intensive treat and extend regime to a fixed dosing regimen

PROTOCOL NUMBER: R1448/31/2017

PROTOCOL VERSION: 5.0
PROTOCOL DATE: 26 July 2019

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PROTOCOL SIGNATURE PAGE

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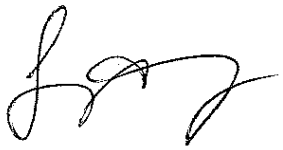
Sponsor Name: NMRC CTG-ICT

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: A/Prof Gemmy Cheung Chui Ming

Principal Investigator Signature: _____  _

Date: _____26 July 2019_____

1. BACKGROUND AND RATIONALE

Age related macular degeneration (AMD) is one of the leading causes of blindness worldwide. In its exudative or wet form, choroidal neovascularization (CNV) causes an exudative maculopathy resulting in sudden loss of vision with severe effects on patients' quality of life. Intravitreal injections of anti vascular endothelial growth factor agents (anti-VEGF) agents have become the mainstay of treatment for AMD CNV and has been shown to have favorable outcomes in most AMD CNV subtypes. In the Asian population however, a particular subtype called polypoidal choroidal vasculopathy (PCV), which affects about 50% of exudative maculopathy, has been shown to have less favorable response to anti-VEGF therapy. The EVEREST trial, a randomized controlled trial which compares the efficacy of photodynamic therapy (PDT) with or without ranibizumab for treatment of PCV showed that PDT with or without anti VEGF improved polyp closure rate on angiographic assessment but this trial did not take into account vision as a primary end point.

There is emerging evidence for the use of aflibercept monotherapy in PCV. Reports range from small case series and retrospective studies to larger prospective studies. Recently, the PLANET study showed that monotherapy of aflibercept resulted in similar letter gains in visual acuity as compared to combination treatment with PDT at 1 year. Polyp closure rate was also similar between the two groups at 38.9% with monotherapy and 44.8% with combination therapy. The VAULT and APOLLO studies show consistent results with this and suggest vision and anatomical improvements with 66-72% polyp closure in 1 year. These trials however, use a fixed dosing regime for 12 months of 3 monthly loading doses of 2mg aflibercept followed by fixed dosing every 8 weeks (2q8) totaling 7 injections in 1 year.

In the clinical setting, a significant an unmet need in the management of PCV is a tailored treatment regime. Here we propose a treatment regimen based on disease activity for PCV with aflibercept mono therapy. A limitation of the 2q8 regime is that it is fixed and does not vary regardless of polyp closure or anatomical outcome at the first time point of assessment (month 3). We hypothesize that after the initial 3 monthly injections of aflibercept, about 50% of PCV will close and become quiescent, and in the remaining 50%, a further 3 monthly injections will increase overall polyp closure rate. After a loadings phase of either 3 or 6 months, all eyes will start on a treat and extend regime (T&E), with a minimum period of 8 weeks and a maximum of 12 weeks between treatments with 2 week increments if PCV remains quiescent. The proposed study aims to evaluate the efficacy of a modified treat and extend regime based on disease activity with aflibercept monotherapy for PCV.

This study will be the first to assess not only the T&E regime in PCV but also the use of activity to guide treatment early in the disease to ensure more intense intervention in non-responsive patients. The results from this study will add to the existing evidence that monotherapy with aflibercept for PCV is a viable option and build on refining treatment regimes for real world clinical settings. In clinical practice, these results will also provide clinicians with the confidence to use the T&E regime in their patients with PCV allowing for a more balanced treatment regime with longer follow up in patients with quiescent disease yet not compromising on response.

We also aim to build on our previous work, and aim to evaluate longitudinal choroidal changes and their correlation with functional outcomes using swept source OCT-A in patients with PCV treated with aflibercept.

2. HYPOTHESIS AND OBJECTIVES

Specific Aim 1: To compare the efficacy and safety of intravitreal aflibercept in eyes with PCV using a modified treat and extend regime with versus fixed dosing regimen

Hypothesis: That after the initial 3 monthly injections of aflibercept, about 50% of PCV will close and become quiescent, and in the remaining 50%, a further 3 monthly injections will increase overall polyp closure rate.

Specific Aim 2: To evaluate longitudinal choroidal changes and their correlation with functional outcomes using swept source OCT-A in patients with PCV treated with aflibercept.

Hypothesis: That aflibercept will result in choroidal vascular changes, specifically a reduction in haller's layer vessel calibre which forms the basis of treatment response.

Seondary Aim: To analyze whether imaging parameters (e.g. choroidal thickness, pachyvessels, choroidal hyperpermeability, PCV subtype) influence the visual outcome at month 12.

3. EXPECTED RIKS AND BENEFITS

The benefits to the patients will be a tailored treatment regimes based on disease activity for PCV. Patients will have more individualised treatment specific to their disease progression and may either benefit from 1) less injections with prolonged intervals if quiescent or 2) a more intensive treatment initially to arrest the development of more active disease progress. The recruited patient will also have a direct benefit in receiving free intravitreal aflibercept treatment during the course of the study regardless of treatment arm. Risks to the patient would be the adverse events from the intravitreal injections like endophthalmitis, cerebral or cardiac complications, which are very rare.

4. STUDY POPULATION

4.1. List the number and nature of subjects to be enrolled.

A minimum of total 55 study participants aged 45 years and above diagnosed with PCV and are treatment naïve. 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.

4.2. Criteria for Recruitment and Recruitment Process

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.

4.3. Inclusion Criteria

Participant

1. Male or female study participants, age >=45 years of age at the time of informed consent.
2. Best corrected ETDRS visual acuity score between 78 to 25 (ie 20/32 to 20/320)
3. Diagnosis of PCV based on ICGA
    a. Presence of intra retinal or subretinal fluid/blood at the fovea as seen on OCT
    b. 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 (vPDT), regardless of indication
*NO other previous treatment for nAMD, except oral supplements and traditional Chinese medicine

4. Media clarity, pupillary dilation and individual cooperation sufficient for study procedure including fundus photography.
5. Able and willing to provide informed consent.

4.4. Exclusion Criteria

Participant

1. 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).
2. Participation in an investigational trial within 30 days of enrolment which involves treatment with unapproved investigational drug
3. Known allergy to any component of the study drug.
4. 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.*
5. 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.
6. Systemic anti-VEGF or pro-VEGF treatment within four months prior to randomization or anticipated use during the study.

Study Eye

1. Eye with intra retinal or subretinal fluid due to other causes than PCV
2. 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.)
3. 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).
4. Any intraocular surgery within 3 months of enrollment
5. Treatment with intra vitreal corticosteroids
6. History of retinal detachment or surgery for retinal detachment
7. History of vitrectomy
8. History of macular hole
9. Evidence of vitreomacular traction that may preclude resolution of macular edema > 4 disc areas of intra/sub retinal hemorrhage
10. Aphakia
11. Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis

Other Eye

1. Active intraocular inflammation
2. History of uveitis

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

Prospective, 2-arm, Non-inferiority, interventional study to evaluate the efficacy of intravitreal aflibercept in eyes with PCV using a disease activity guided T&E regimen versus fixed dosing regimen.

Duration for each participant: 52 weeks

Medical record of participants will be reviewed 1 year after they completed the study. This is to better understand the percentage of patients that continue to require standard of care therapy after exiting study. Further to that, patients' clinical status (e.g. anatomical outcomes) at the end of 1 year may influence future treatment needs.

Randomization/Stratification

Patients will be randomized to 2 treatment groups (2Q8, and T&E) using a ratio of 1:3; 2Q8: T&E. Randomization will be performed using a blocked randomization method. This will be carried out by drawing lots for randomization in blocks of 20 for 40 participants. The balance lots for randomization for 12 participants will make up the difference. The addition of the 3 study participants is to replace those who have been withdrawn from the study. Thus, no randomization is required for these 3 study participants.

Study Treatment Groups and Regimen:

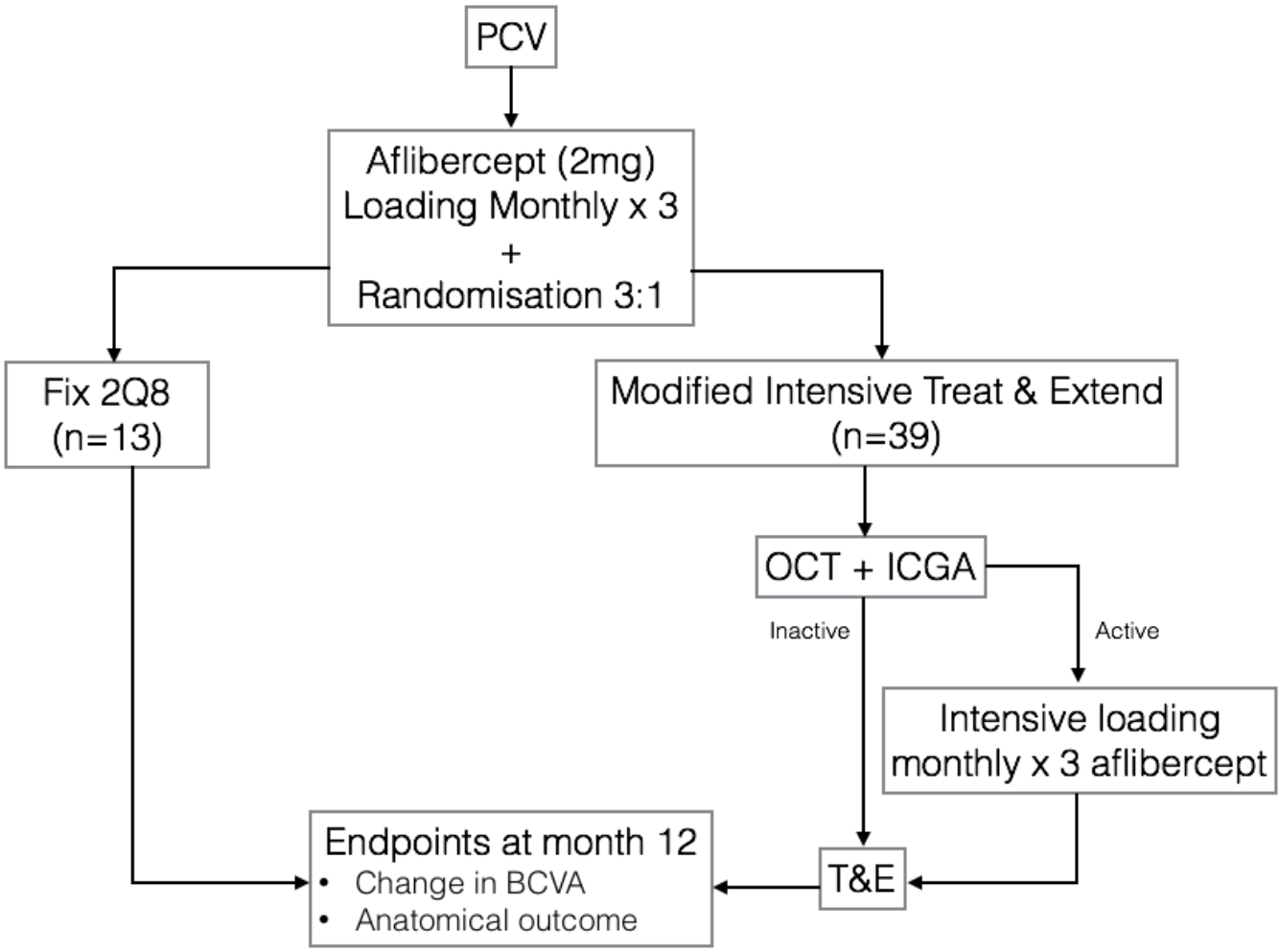
All patients fitting the recruitment criteria will undergo 2mg aflibercept administered at baseline (day 1) and weeks 4 and 8 (loading phase) followed by:

1. Fixed dosing group (2Q8): fixed doses at 8 week intervals through to week 52

2. Treat and Extend group (T&E): Reassessment at week 12 (month 3) by repeat examination for disease activity by OCT and ICGA. Subsequent treatment regime will depend on disease activity at this point.

    a. If disease is considered inactive, as defined by a dry OCT and complete polyp closure on ICGA, patients will undergo a treat and extend protocol. The next dose would occur at week 16 (8 week interval from last dose at week 8) and each subsequent dose and visit will be extended by 2 weeks up to a maximum interval of 12 weeks and minimum interval of 8 weeks between treatments if disease remains quiescent. If signs of activity are noted at any visit point, dose and visit interval will be reduced by 2 weeks. (Activity is signified by subretinal or intra retinal fluid and/or blood seen on OCT or clinical examination.)

    b. If disease is still active, patients will receive additional doses at week 12, week 16 and week 20 (intensive loading). Thereafter, patients will start on the treat and extend protocol as described above.



Study Visits and Procedures

Screening Evaluation
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.

An assessment of visual related quality of life will be performed using the impact of visual impairment (IVI) questionnaire.

Screening Testing Procedures
The following procedures are needed to assess eligibility and/or to serve as baseline measures for the study.

If a procedure has been performed (using the study technique and by delegated personnel) as part of usual care, it does not need to be repeated specifically for the study if it was performed within the defined time (within 21 days prior to baseline) windows specified below.

1. Best-corrected Visual Acuity: BCVA will be measured using the ETDRS VA protocol following manifest refraction.
2. Optical Coherence Tomography/ OCT Angiography: OCT and OCTA will be performed. Both standard and enhanced depth imaging scans will be performed.

3. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy (within 21 days prior to randomization).
4. Fundus Photography
5. Fundus fluorescein and Indocyanine Green angiography: FFA and ICGA will be performed.

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

- Diagnosis of PCV based on ICGA.
- Presence of activity clinically as evidence by presence of haemorrhage, edema.
- Presence of activity as evidence by intra retinal or sub retinal fluid on OCT.

Visit Schedule

All patients will have visits at screening, baseline (day 1), and every 4 weeks until week 8. Subsequent visits will depend on regime arm and disease activity as assessed at week 12.

Maximum and minimum visits are summarised in the table 2 below.

1 year after study completion

Medical records inclusive of VA, treatment received and ocular imaging scans such as OCT, OCTA, Fundus photography, FFA and ICGA will be reviewed.

Table 1: Study Visits & Procedures

Study Procedure										**Last visit**	**1 year after completion**
Visit	**1 (Screen)**	**2(BL)**	**3**	**4**	**5**			**7(8^)**	**6(7^)-N**	**N+1**	
Month	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**6-12**	**12**	
Week	**- 3 to 0**	**0**	**4**	**8**	**12**	**16**	**18**	**24-52**	**12-52**	**52**	
Day (± 7), except Visit 2 (±3)	**-21 to 0**	**1**	**29**	**57**	**85**	**113**	**127**	**141**	**113-337**	**365**	
Informed consent	●										
Demographics	●										
Questionnaires	●									●	
Medical / ophthalmic history	●										
Inclusion / exclusion	●	●									
Study drug injection											
Fixed dosing arm		●	●	●	Fixed dosing every 8 weeks						
T&E: Complete closure at month 3		●	●	●	Treat and Extend X X X X						

T&E: Incomplete closure at month 3		●	●	●	●*	●*	●*	Treat and Extend			
BCVA LogMAR letter score	●	●	●	●	●	At every visit		●	At every visit	●	
Indirect ophthalmoscopy		●	●	●	●			●		●	
Slit lamp		●	●	●	●			●		●	
IOP	●	●	●	●	●			●		●	
OCT	●	●	●	●	●			●		●	
Adverse events	●	●	●	●	●			●		●	
Colour FP	●	-	●	●	●	-	-	●	-	●	
FA	●	-	-	-	●	-	-	●	-	●	
ICGA	●	-	-	-	●	-	-	●	-	●	
Review of medical record											●

BL – Baseline visit

Screen – screening visit

● Will occur

* If PCV is active at week 12, 3 more injections will be administered increasing visit by 1 within first 24 weeks (see MAX treatment table 2)

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

Table 2: schedule of procedures

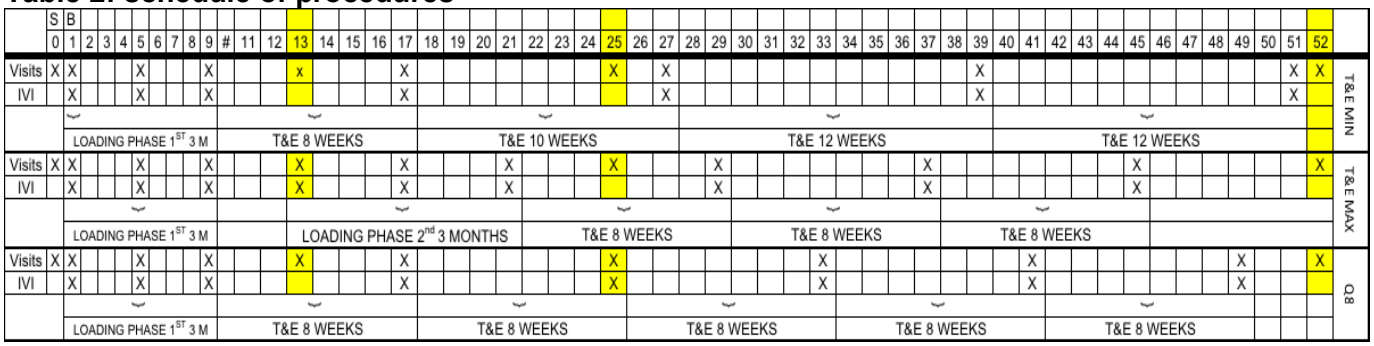


Table 3: maximum and minimum visits including intravitreal injections for each regime

Regime		VISITS/PATIENT	INJECTIONS/PATIENT
T&E (N =39)	Minimum	11	7
	Maximum	12	9
Q8 (N=13)		11	8

<u>Treatment Procedures</u>

Intravitreal Injections

Aflibercept (Eylea)

Study eyes will receive a dose of 2mg in 0.05 ml of aflibercept.

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 anesthetic, followed by a povidone iodine prep of the conjunctiva. (Instill 5% povidone iodide on to the ocular surface and allow adequate time prior to injection)

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 5-10% 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).

IOP measurement post-injection is not mandatory. While small volume injections (0.05ml) are unlikely to cause IOP rise, it should be considered in patients with ocular hypertension or glaucoma, and in all cases where patients 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. Patients 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 three weeks 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.

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.

Warnings and Precautions

Injection Procedure-related Reactions

Treatments such as aflibercept that are administered via intravitreal injections can be associated with a number of adverse events. These include conjunctival haemorrhage, conjunctival hyperaemia, eye irritation, eye pain, eye pruritus, endophthalmitis, foreign body sensation in eyes, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, increases in IOP, vitreous detachment, and iatrogenic traumatic cataract.

Intraocular Inflammation, Endophthalmitis, and Retinal Detachments

Intravitreal injections have the potential to be associated with intraocular inflammation, infectious and non-infectious endophthalmitis, and retinal detachments which could be sight-threatening. Proper aseptic injection technique should always be used when administering aflibercept. In addition, patients should be monitored following the injection to permit early treatment should inflammation, infection, or retinal detachment occur. Patients should be informed that in the days following administration of aflibercept intravitreally, patients are at risk for the development of endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a worsening in vision, the patient should seek immediate care with their ophthalmologist.

Increases in Intraocular Pressure

Increases in IOP have been noted following intravitreal injection with anti-VEGF agents. The increase in IOP is typically transient in nature and is probably due to the volume increase in the eye after injection. Therefore, IOP as well as the perfusion of the optic nerve head should be monitored and managed appropriately following the intravitreal injection.

Cataract Formation

Intravitreal injections have the potential to be associated with iatrogenic traumatic cataract formation.

Anti-VEGF Agents Class Effects

Hypertension, non-ocular hemorrhage and thromboembolic events have been reported with systemic anti-VEGF therapy. There is a potential risk of arterial thromboembolic events following intravitreal use of inhibitors of VEGF. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown causes).

Study Participant Withdrawal and Losses to Follow-up

A study participant has the right to 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.

Discontinuation of Study

The study may be discontinued by the Data and Safety Monitoring Committee [DSMC] prior to the preplanned completion of follow-up for all study participants.

Study Participant Reimbursement

The study will be providing the study participant with $20.00 per completed protocol visit to cover travel and other visit-related expenses.

6. SAFETY MEASUREMENTS

6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

6.2. Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

Reporting of adverse events involves the Principal Investigator submitting to 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 a monthly basis for Standard Aggregate Adverse Event (AE) Safety Data reports.

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 not 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. Best corrected visual acuity (by visit per subject)
    - ≥ 15 letters decrease from baseline at any visit

6.3. Safety Monitoring Plan

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.

6.4. Complaint Handling

Complaints will be handled by the PI and study coordinators and if required the Quality Assurance team at the Singapore National Eye Centre

7. DATA ANALYSIS

7.1. Data Quality Assurance

The Investigator(s)/ Singapore National Eye Centre will permit study-related monitoring audits, MCRC and or EC review and regulatory inspection(s), providing direct access to source data/ document.

7.2. Data Entry and Storage

Research data will be stored in excel/ word format and encrypted with password. It will be kept in controlled shared folder where confidentiality and participant privacy will be maintained. The data will be coded and the participants will be de-identified and the master list will be encrypted with the password. Case files will be under lock and key, with restricted access to the key, as defined within the study delegation log.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

Mean difference of Best corrected visual acuity at month 12 will be compared between treatment arms looking for non inferiority between treat and extend regimen and fixed dosing regimen.

T test will be used to assess the change in mean BCVA between groups.

Primary outcome: BCVA as outcome

Assumptions:

1. No prior data available for T&E regiment for treatment of PCV with Aflibercept
2. Mean Standard deviation of difference of letters between baseline and final outcome in VAULT study is 4.1 letters
3. 3:1 N ratio of T&E versus fixed dosing

Based on the above assumptions with 80% power and 95% confidence,

If n=13 for fixed dosing (total n = 52)

Minimum difference of **3.9 letters** can be shown

Secondary Outcome: Proportion of closure as outcome

Assumptions:

1. Based on PLANET study results, we estimate the polyp closure rate in the fixed dosing arm will be 40% (Monotherapy closure rate).
2. 3:1 N ratio of T&E versus fixed dosing

3. Non inferiority margin, δ set at 10%*

*statistically significant differences between the proportions may not be of interest unless the difference is greater than a threshold, δ

To detect polyp closure rate of 70% in the T&E arm, with 80% power and 95% confidence, we submit that a sample size of 39 in the T&E arm will be required.

8.2. Statistical and Analytical Plans

The proportion of study patients achieving positive response in primary outcome will be estimated with 95% confidence interval. Summary statistics will be tabulated to describe patient demographics and characteristics. Statistical analysis will be performed using standard statistical software. Outcome at month 12 will be compared to baseline. In addition, we will use linear mixed-effect model to analyze longitudinal data of visual acuity over the first year to account for the repeated measurements on the same eye. Both random and fixed effects of number of injections will be added to control the heterogeneous effect among eyes. Stepwise model selection (forward and backward selection) will be performed to investigate the effect on visual acuity at month 12, from a set of variables, including age, gender, vision at baseline and follow up, change of vision and OCT thickness. Binary or linear regression analysis with multivariate models will be performed on imaging features to determine association with 12 month visual outcomes.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator(s)/ Singapore National Eye Centre will permit study-related monitoring audits, MCRC and or EC review and regulatory inspection(s), providing direct access to source data/ document.

11. ETHICAL CONSIDERATIONS

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 Guideline for Good Clinical Practice (GCP) and the applicable regulatory requirements.

This final study 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), prior to enrolment of any patient into the study.

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

11.1. Informed Consent

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.

11.2. Confidentiality of Data and Patient Records

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 SERI 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.

12. PUBLICATIONS

Please refer to the SERI publication policy

13. RETENTION OF STUDY DOCUMENTS

The research data will be stored for at least 15 years and then destroyed/deleted.

14. FUNDING and INSURANCE

Grant funding from NMRC CTG-ICT.