Eye Co Pty Ltd

A Phase Ib, study of safety and tolerability of Intravitreal Fludrocortisone Acetate (FCA) in Patients with Geographic Atrophy (GA)

Protocol Number:	EC-FCA-001
National Clinical Trial (NCT) Identified Number:	TBD
Principal Investigator:	
Sponsor:	Eye Co Pty Ltd 82 Birriwa Road Bywong NSW 2621
Funded by:	Eye Co Pty Ltd.
Version and Version Number:	Version 1.3
Date:	22 January 2020

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1	Total GA area must be ≥ 1.9 and ≤ 22 mm^2 (1 and 10 disc areas (DA) respectively), determined by screening images of FAF.	Total area of GA inclusion has been extended. As a phase I study of safety and efficacy in the treatment of GA, extending the inclusion area will allow a greater sample population and better

	If GA is multifocal, at least one focal lesions must be ≥ 1.00 mm^2 (0.5 DA).	assessment of safety and action on GA
1.1	History of IVT injection of steroids at any time.	A history of IVT injection has been further clarified to include steroid injections only, as anti-VEGF IVT injections are mediated by a different pathogenetic process to not have credible effect to obscure results with the IP.
1.1	Deletion of "but the numbers chosen are considered adequate for assessing the study objectives"	This clarification was recommended by the DSMB which does not affect the sample size or conduct of the study

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INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

ADDRESS:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable state, local and federal regulatory requirements.
- The protocol, informed consent forms), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled.
- Maintain all information supplied by Eye Co Pty Ltd in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.
- I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phase Ib, study of safety and tolerability of Intravitreal Fludrocortisone acetate (FCA in Patients with Geographic Atrophy (GA)
Sponsor:	Eye Co Pty Ltd
Protocol Number, Version and Date:	EC-FCA-001/ Version 1.3 / 22 January 2020
Investigational Product, Dose and Route of Administration:	Fludrocortisone acetate (FCA) 1mg/0.1ml & 2mg/0.1ml Intravitreal (IVT) injection
Rationale for dose:	Single dose of 0.1 ml in a concentration of 1mg/0.1 mL and 2mg/0.1mL was selected based on previous pre-clinical model (Kivilcim et al). There were no signs of retinal toxicity on slit-lamp examination, indirect ophthalmoscopy, or by light microscopy in all eyes injected with 400µg/0.1mL, 1mg/0.1mL and 2mg/0.1mL. However, it was reported 1 case of intravitreal haemorrhage in 4 mg/0.1 mL. Systemic injection of Fludrocortisone acetate has serious mineral corticoid and glucocorticoid side effects such as hypertension, potassium loss, Cushingoid changes, etc. Intravitreal injection fludrocortisone acetate may avoid systemic side effects.
Objectives:	To determine safety and tolerability of a single dose intravitreal (IVT) injection of 1mg/0.1mL and 2mg/0.1mL FCA in subjects

with GA secondary to Age-Related Macular Degeneration (AMD).

Study Population: Study population will comprise of patients with GA secondary to AMD in both eyes with no previous treatment. The study is planned to enrol up to 9 participants.

Study Design: This study is planned to enrol 9 participants to assess dose escalation based on a 3+3 algorithm. Enrolment will stop if > 2 patients experience dose-limiting toxicity at any time during the study. Dose-limiting toxicity is defined by intraocular inflammation, elevated IOP, reduced vision (loss of ≥15 letters), or haemorrhage within 28 days after injection.

Part 1 involves a single participant to assess safety and tolerability of 1mg/0.1mL FCA. This participant will be followed for up to 28 days and reviewed by a safety review committee prior to the recruitment of a further 2 participants treated with 1mg/0.1mL FCA totalling in 3 participants in the first cohort.

Part 2 involves a single participant to assess safety and tolerability of 2mg/0.1mL FCA. This participant will be followed for up to 28 days and reviewed by an independent safety review committee prior to the recruitment of a further 5 participants treated with 2mg/0.1mL FCA totalling in 6 participants in the second cohort.

The sample size (n=9) chosen for this study was selected without formal statistical justification. The sample size was determined on the basis of practical and logistical considerations for a pilot study and not based on statistical power with regard to hypothesis testing or precision with regard to parameter estimation.

Description of Study Intervention:	Fludrocortisone acetate (9-α-Fiuoro-11 β. 17 α, 21-trihydroxy-4-pregnene-3, 20 dione acetate) is a synthetic steroid possessing a potent mineralocorticoid effect and a high glucocorticoid activity. The physiologic effects of Fludrocortisone acetate are similar to hydrocortisone but much more potent. FCA has a glucocorticoid activity ten times higher than cortisol and a mineralocorticoid effect 250 times higher than cortisol. Addition of fluorine to C-9 of cortisol gives fludrocortisone a markedly increase in glucocorticoid, mineralocorticoid and anti-inflammatory potency. The drug will be administered via intravitreal injection.
Study Duration:	6-months' recruitment and 6-month follow-up period.
Participant Duration:	Participants will be on the study for 6 months. **Screening:** up to 14 days **Treatment**: 1 day **Follow-up:** 6 months
Inclusion Criteria:	Unless specified otherwise, ocular specific inclusion criteria apply to the study eye only.

1. Willing and able to give consent prior to any specific procedures being performed.
2. Male or Female.
3. Age ≥ 50 years.
4. Best corrected visual acuity (BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (20/320 Snellen equivalent).
5. Diagnosis of GA of the macula secondary to AMD in both eyes, confirmed within 14 days prior to dosing by the PI using Fundus Autofluorescence (FAF) images, as well as the following criteria:

   a. Total GA area must be ≥ 1.9 and ≤ 22 mm^2 (1 and 10 disc areas (DA) respectively), determined by screening images of FAF.
   b. If GA is multifocal, at least one focal lesions must be ≥ 1.00 mm^2 (0.5 DA).
   c. GA can be completely visualized on the macula centered image.
   d. GA must be able to be photographed in its entirety.
   e. GA must be able to be measured separately from any areas of peripapillary atrophy.
   f. Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (i.e. pattern = none) is exclusionary. See Holz et al. 2007[1]
6. Female subjects must be:
   a. Women of non-childbearing potential (WONCBP), or
   b. Women of childbearing potential (WOCBP) with a negative pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study.
7. Males with female partners of childbearing potential must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study.
8. Willing and able to give informed consent.

Note: If both eyes meet the inclusion criteria, the eye with the best visual acuity at the screening visit will be designated as

the study eye. If both eyes have the same visual acuity, the right eye will be used as the study eye.

Exclusion Criteria: Unless specified otherwise, ocular specific exclusion criteria apply to the study eye only.

1. GA due to causes other than AMD such as Stargardt disease, cone rod dystrophy or toxic maculopathies like plaquenil maculopathy.
2. Spherical equivalent of the refractive error demonstrating > 6 dioptres of myopia or an axial length of >26 mm.
3. Evidence of exudative (wet) AMD including evidence of retinal pigment epithelium rips or evidence of neovascularization anywhere in the retina based on fluorescein angiogram as assessed by the PI in either eye within 12 months.
4. Retinal disease likely to confound visual performance or be affected by intraocular steroid.
5. Any ophthalmologic condition that reduces clarity of the media and that, in the opinion of the investigator interferes with ophthalmologic examination (e.g. advanced cataract or corneal abnormalities).
6. Any ophthalmologic condition that prevents adequate imaging of the retina judges by the PI.
7. Intraocular surgery (including lens replacement surgery) within 3 months prior to dosing.
8. Aphakia or absence of the posterior capsule. Previous violation of the posterior capsule is also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior

posterior chamber intraocular lens implantation and at least 60 days prior to Day 0.

9. Any ophthalmologic condition that may require surgery during the study period.
10. Glaucoma or family history of glaucoma.
11. Any contraindication of IVT injection including current ocular or periocular infection.
12. History of uveitis or endophthalmitis.
13. History of choroidal neovascularization (CNV) in either eye.
14. History of IVT injection of steroids within 12 months.
15. Participation in another interventional clinical study, or use of any experimental treatment for AMD or any other investigational new drug within 6 weeks or 5 half-lives of the active (whichever is linger) prior to the start of study treatment. Note: clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary.
16. Systemic conditions that are applicable to the use of fludrocortisone such as hypertension, and fungal infections.
17. Medical or psychiatric conditions that, in the opinion of the investigator, make consistent follow-up over the study period unlikely, or in general a poor medical risk because of other systemic diseases or active uncontrolled infections.
18. Any screening laboratory value (haematology, serum chemistry or urinalysis) that in the opinion of the investigator is clinically significant and not suitable for study participation.
19. Hypersensitivity to fluorescein.

Endpoints:

The primary endpoints of the study are safety and tolerability of intravitreal (IVT) dose of Fludrocortisone acetate in subjects with geographic atrophy (GA) secondary to Age-Related Macular Degeneration (AMD), based on assessment of vital signs, clinical safety labs, and adverse events.

Primary Safety Endpoint

- Number and severity of local and systemic treatment emergent events (TEAE).

Secondary Endpoints

- The change in geographic atrophy (GA) lesion size from baseline to Month 6 as measured by FAF.
- Change in best corrected visual acuity (BCVA).
- Change in low luminance best corrected visual acuity (LL-BCVA).
- Relationship between GA lesion size changes and changes in BCVA.
- Increase in intraocular pressure (IOP).

Pharmacokinetic (PK) parameters

- Exposure after single dose Fludrocortisone acetate IVT injections.
- Serum maximum observed concentration.
- Time to maximum measured concentration
- Terminal elimination half-life.

Planned Interim Analysis	There is no formal interim analysis planned for this study. However, a data safety monitoring board (DSMB) for safety data review will be planned for this study.
Analysis Populations	The following analysis populations are planned: • Safety Population: All enrolled participants IVT Fludrocortisone acetate will be included in the safety population. • Intention-to-treat (ITT) Population: all enrolled participants who received IVT Fludrocortisone acetate and had at least one efficacy measurement taken after dosing will be included in the ITT population.
Statistics Analyses	**Safety Analysis** Statistical methods for the safety analyses will be primarily descriptive in nature. Listings and summaries for all safety data will be presented using the Safety Population. Descriptive statistics (mean, SD, median, minimum and maximum) will be calculated for summaries of continuous safety data and frequency counts and percentages (where appropriate) will be calculated for summaries of discrete/categorical safety data. Safety data, including vital signs, clinical safety labs and adverse events, will be summarised. Change from baseline will be included in summary tables for vital signs and laboratory parameters. All laboratory data will be included in the data listings and all test values outside the normal range will be flagged. Physical examinations will be listed for each participant. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and data will be summarised by System Organ Class and preferred term.

Efficacy Analysis

Exploratory analysis will be performed for the best-corrected visual acuity (BCVA) and will be scored with reference to the Early Treatment Diabetic Retinopathy Score (ETDRS letters). Geographic atrophy lesion size will be measured in mm^2 by fundus autofluorescence imaging.

Descriptive statistics (mean, SD, median, minimum and maximum) will be summarised for ETDRS letters and GA area in mm2 observed values and change from baseline at each post-injection visit. Exploratory analysis of ETDRS letter change and GA lesion size over time will be assessed by using a mixed model. The least squares mean of ETDRS and GA lesion size change from baseline and its 95% confidence interval at each visit will be estimated. Similar analyses will be conducted for intraocular pressures.

Categorical efficacy endpoints such as slit lamp biomicroscopy exam findings, dilated ophthalmoscopy exam findings, colour fundus photography and OCT findings will be summarised descriptively by frequency count and percentage (proportion) as appropriate.

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -14 to -1	Baseline Visit 1, Day 0	Study Visit 2 Day 1 +/-1 day	Study Visit 3 Day 7 +/- 1 day	Study Visit 4 Day 14 +/-1 day	Study Visit 5 Day 28 +/-1 day	Study Visit 6 Day 60 +/-1 day	Study Visit 7 Day 90 +/-1 day	Final Study Visit 8 Day 150 +/-1 day
Informed consent	X								
Demographics	X								
Medical history	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse event review			X	X	X	X	X	X	X
Administer study intervention		X							
Physical exam	X	X			X			X	X
Vital signs	X	X	X	X	X	X	X	X	X
Best corrected visual acuity (BCVA)	X	X	X	X	X	X	X	X	X
Height and Weight	X						X		X
Visual Function Questionnaire (VFQ-25)		X							X
Goldmann Intraocular Pressure (IOP)	X	X	X	X	X	X	X	X	X
Slit lamp biomicroscopy, incl. lens grading	X	X	X	X	X	X	X	X	X
Dilated ophthalmoscopy	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X
FAF and NIFR	X	X	X	X	X	X	X	X	X
Colour Fundus Photography	X						X		X
Fluorescein angiogram	X								X
Haematology & Urinalysis	X	X		X		X			X
Serum chemistry [a]	X	X		X		X			X
Urine Pregnancy test [b]	X								X
Pharmacokinetic sampling		X		X		X			X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.

b: Serum pregnancy test (women of childbearing potential).

1.3 ABBREVIATIONS

AE	*Adverse event*
AMD	*Age-related macular degeneration*
BCVA	*Best corrected visual acuity*
DCFP	*Digital colour fundus photography*
CNV	*Choroidal neovascularization*
CRC	*Central reading centre*
CRF (eCRF)	*Case report form (electronic CRF)*
CRO	*Contract research organization*
DSMB	*Data safety monitoring board*
CTCAE	*Common Terminology Criteria for Adverse Events*
ETDRS	*Early treatment diabetic retinopathy score*
FA	*Fluorescein angiogram*
FAF	*Fundus autofluorescence*
FCA	*Fludrocortisone acetate*
FSH	*Follicle-Stimulating Hormone*
GA	*Geographic atrophy*
GCP	*Good Clinical practice*
HIPAA	*Health Insurance Portability and Accountability Act*
ICF	*Informed consent*
IEC	*Independent Ethics Committee*
IOP	*Intraocular pressure*

IRB	*Institutional Review Board*
ITT	*Intention-to-treat*
IVT	*Intravitreal*
LFT	*Liver Function test*
LH	*Luteinising Hormone*
LL-BCVA	*Low luminance best corrected visual acuity*
LOCS II	*Lens Opacities Classification Systems III*
MedDRA	*Medical dictionary for Regulatory Activities*
Mg	*Milligram*
mITT	*Modified intention to treat*
ML	*Millilitre*
mmHg	*Millimetre of mercury*
NIFR	*Near-Infrared Fundus Reflectance*
OCT	*Optical coherence tomography*
PI	*Principal investigator*
PK	*Pharmacokinetics*
QC	*Quality control*
RBC	*Red blood cell*
RPE	*Retinal pigment epithelium*
SAE	*Serious adverse event*
SD-OCT	*Spectral-domain optical coherence tomography*
SMC	*Safety monitoring committee*
SoA	*Schedule of Activities*

TEAE	*Treatment emergent events*
VA	*Visual acuity*
VEGF	*Vascular endothelial growth factor*
VFQ	*Visual Function Questionnaire*
WBC	*White blood cell*
WOCBP	*Women of child bearing potential*
WONCBP	*Women of non-child bearing potential*
YAG	*Yttrium aluminium garnet*

2 INTRODUCTION

2.1 BACKGROUND

This study is being conducted for the clinical development of intravitreal Fludrocortisone acetate (FCA) for advanced Age-related Macular Degeneration (AMD) (geographic atrophy [GA]). The trial will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will be comprised of adult male and female subjects with GA secondary to AMD.

2.2 AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration is the leading cause of severe vision loss in people over the age of 65 in the United States and other Western countries[1]. In the United States, about 1.75 million people have the advanced forms of AMD [2, 3]. The early signs of AMD (drusen and pigmentary changes) are common in individuals over age 65 and precede the advanced forms, which are visually devastating. The advanced forms of AMD are classified into either macular neovascularization (neovascular, wet, or exudative AMD) or GA.

Exudative AMD is characterized by the abnormal growth of choroidal vessels into the subretinal space. The subsequent exudation of fluid, lipid and blood causes retinal edema resulting in vision loss and symptoms of metamorphopsia. The growth of these new vessels is accompanied by the proliferation of fibrous tissue; the continued growth of these fibroblastic lesions into the macula results in progressive, severe and irreversible vision loss. Although exudative AMD is only present in about 10% of all AMD cases, the majority (90%) of the severe rapid visual loss due to advanced AMD is attributable to the development of macular neovascularization[4]. Without treatment, most affected eyes will develop poor central vision (20/200) within 12 months. Anti-VEGF agents, such as ranibizumab (Lucentis®), aflibercept (Eylea®) and off-label

bevacizumab (Avastin®), are the current standard-of-care for the treatment of exudative AMD.

Geographic Atrophy is a disease characterized by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and choriocapillaris[4]. Clinically, GA is characterized by islands of dead retinal cells in the back of the eye that gradually expand. Although GA can result in significant visual function deficits in reading, night vision, and dark adaptation, and produce dense, irreversible scotomas in the visual field, the initial decline in VA may be relatively limited if the fovea is spared. When the fovea is involved, GA quickly causes blindness. GA is responsible for approximately 20% of all legal cases of blindness in North America with increasing incidence and prevalence owing to a higher life expectancy.

The presence of drusen and pigmentary abnormalities in the central macula is the main ocular risk factor for late age-related macular degeneration. The greater the area of drusen at the macula the greater the risk of progression to loss of vision. Using the direct ophthalmoscope or a slit lamp these early changes can be detected.

AMD is a highly complex disease that is affected by multiple factors, such as ageing, genetic predisposition, environmental elements, oxidative stress and inflammatory effects [2, 5, 6]. Smoking, age, alcohol consumption, diet and obesity are important risk factors related to oxidative stress [6, 7]. High body mass index, cardiovascular disease, hypertension and a variety of dietary patterns are risk factors less consistently[8]. Several single-nucleotide polymorphisms (SNPs) that confer increased or decreased risk of inflammation have been identified. They include the well-recognized *complement factor H* (CFH), CX3CR1, *Toll-like receptor* 3 (TLR3), TLR4, and *interleukin 8* (IL-8)[9]. Although AMD is not a classic inflammatory disease, inflammatory cells have an important role in AMD pathogenesis and progression [5, 10, 11]. Evidence has also suggested that some infectious agents are associated with AMD.

Although relatively simple to diagnose through direct visualization augmented with rapid sequence fluorescein angiography, treatment has presented a far greater challenge because the true etiology of AMD is largely unknown [12]. Within the past decade, researchers have introduced many new, potentially promising treatment and prevention

options in an attempt to minimize the damage imparted from AMD. The current standard-of-care for the treatment of exudative AMD are the anti-VEGF agents, such as ranibizumab (Lucentis®), aflibercept (Eylea®) and off-label bevacizumab (Avastin®) [13]. No therapy exists for GA which is usually bilateral and relentlessly progressive. Dexamethasone and triamcinolone acetonide (TA) are the commonly used corticosteroids for macular oedema [14, 15].Most studies showed their effectiveness in improving vision function and reducing macular oedema. Nevertheless, intravitreal injection of corticosteroids carries significant complication risk such as cataract progression, ocular hypertension and endophthalmitis.

Because of the substantial amount of evidence suggesting the underlying role of inflammation in AMD, it is logical to target the specific molecules involved in inflammatory pathways [16, 17]. Corticosteroids were among the first anti-inflammatory drugs evaluated for treating choroidal neovascularization in AMD patients [16]. Although the anti-inflammatory mechanism of corticosteroids is not fully understood, in addition to the anti-inflammatory effects, corticosteroids can directly and indirectly reduce the permeability of choroidal endothelial cells and the outer blood retina barrier, inhibit the activation of matrix metalloproteinase, and suppress vascular endothelial growth factor (VEGF) expression [18]. Because VEGF and inflammatory cells closely interact with each other, inhibition of VEGF might strengthen the anti-inflammatory activity in AMD. The downregulation of inflammatory agents and inhibition of blood vessel permeability are regarded as the main goals of AMD treatment [16].

2.2.1 FLUDROCORTISONE ACETATE

Fludrocortisone acetate (9-α-Fiuoro-11 β. 17 α, 21-trihydroxy-4-pregnene-3, 20 dione acetate) is a synthetic steroid possessing a potent mineralocorticoid effect and a high glucocorticoid activity[19]. FCA is a synthetic corticosteroid with anti-inflammatory and anti-allergic properties. FCA is a mineralocorticoid receptor and glucocorticoid receptor agonist that binds to cytoplasmic receptors, translocates to the nucleus and subsequently initiates the transcription of glucocorticoid-responsive genes such as

lipocortins to inhibit phospholipase A2. This prevents the release of arachidonic acid, a precursor to prostaglandins and leukotrienes, both important mediators in the pro-inflammatory response mechanism. In addition, this agent exerts its mineralocorticoid effect on the distal tubules and collecting ducts of the kidney by inducing permease, an enzyme that regulates Na+ permeability in cells, thereby enhancing Na+ reabsorption and water retention as well as increasing K+, H+ excretion.

2.2.2 CLINICAL DATA

This section is intended to briefly summarise the information on characteristics and safety of Fludrocortisone acetate relevant for the present study. For complete and detailed information refer to the Investigator's Brochure.

The safety and tolerability of oral Fludrocortisone acetate has been determined by a number of clinical studies. Fludrocortisone acetate has been used in the treatment of cerebral salt wasting syndrome [20-22]. It is used primarily to replace the missing hormone aldosterone in various forms of adrenal insufficiency such as Addison's disease and the classic salt wasting (21-hydroxylase deficiency) form of congenital adrenal hyperplasia [23-25]. Due to its effects on increasing Na+ levels, and therefore blood volume, fludrocortisone acetate is the first line of treatment for orthostatic intolerance and postural orthostatic tachycardia syndrome (POTS) [26-28].It can be used to treat low blood pressure.

Fludrocortisone acetate is also a confirmation test for diagnosing Conn's syndrome (aldosterone producing-adrenal adenoma), via the fludrocortisone suppression test. Loading the patient with fludrocortisone would suppress serum aldosterone level in a normal patient, whereas the level would remain elevated in a Conn's patient [29]. The fludrocortisone suppression test is an alternative to the NaCl challenge (which would use normal saline or NaCl tablets).

2.2.3 ANIMAL STUDIES

An animal study was conducted to evaluate the safety and efficiency of Fludrocortisone acetate after intravitreal injection into the vitreous cavity [30]. Surgeries were performed on the eyes of 25 New Zealand white rabbits. Fludrocortisone acetate was titrated using sterile BSS solution to the following concentrations: 4 mg/ 0.1 ml, 2 mg/ 0.1 ml, 1 mg/0.1 ml, and 400 µg/0.1 ml, which were injected intravitreal into one eye of twenty-five rabbit eyes. The control eyes received 0.1 ml of sterile BSS. All animals were examined before and after injection using indirect ophthalmoscope and slit-lamp biomicroscopy. Electroretinography (ERG) was performed on all animals prior to intravitreal injection and two weeks after injection. The animals were re-examined at this time by indirect ophthalmoscope and slit-lamp biomicroscopy and were euthanized. Their eyes were enucleated and examined with light microscopy.

Outcomes from these in vivo tests were positive for the application of intravitreal Fludrocortisone acetate. In multiple measurements, up to 40 days of observations, the slit lamp biomicroscopy and indirect ophthalmoscopy did not show any evidence of significant inflammation in the anterior or posterior segment of the eye in either the control or treatment groups. Intraocular pressure (IOP) was normal across all groups.

Histological examination of retinal sections, under light microscopy, revealed that the integrity of the retinal layers appeared preserved with no evidence of toxicity or vacuolization except for one eye in the 4mg group. All aggregates of Fludrocortisone acetate disappeared by 22 +/-8 days in the 2-mg group, and 33 +/-7 days in the 4-mg group.

In ERG testing, one eye injected with 4mg/0.1ml exhibited decreases in ERG output. All other eyes had a normal ERG. These findings represent promising results for intravitreal Fludrocortisone acetate that is clinically suitable for both short-term and long-term use.

Data from the light-damage model of dry AMD in mice showed FCA delivered in Kenalog vehicle resulted in significantly less cell death, and significantly fewer macrophages that carry the IBA1 marker 7 days later. Histology shows that the animals

treated with FCA have a much thicker outer nuclear layer. Treated animals have a significantly more robust Electroretinogram A-wave (Photoreceptor function) and B-wave (inner retinal function).

2.3 RATIONALE

2.3.1 RATIONALE FOR THIS STUDY

Fludrocortisone acetate is available in tablet form (0.1 mg) from the PBS and so is approved for use in humans in Australia. In a study of 121 patients Gonzalez [31] reported excellent outcomes with fludrocortisone for anterior segment lesions. He cited 4 previous papers with similar experiences.

There is older pre-clinical data suggesting FCA is effective. Among that is Fitzgerald et al. [32] who found that FCA was superior to TA in a study of phorbol-12-myristate-acetate (PMA)-stimulated monkey choroidal endothelial cells (CECs) in restoring quiescent morphology and reducing membrane permeability. Prof Jan Provis et al. have a large body of new preclinical data that indicates FCA is superior to TA in a rat model of dry AMD. FCA was superior in terms of preventing cell death, macrophage recruitment, and preserving a- and b-wave ERG amplitude.

Kivilcim [33] examined intravitreal FCA in 25 normal rabbits at 4 mg/0.1 ml, 2 mg/0.1 ml, 1 mg/0.1 ml, and 400 µg/0.1 ml. Two eyes at 4 mg/0.1 ml experienced intravitreal haemorrhage and reduced ERG. There were no other problems of reductions in ERG. The smaller volume of the rabbit eye would suggest 4 mg/0.1 ml would be safe in humans. TA is commonly given at 4 mg/0.1 ml so comparing the same doses for each steroid would be sensible.

In the current clinical study fludrocortisone acetate, corticosteroid inhibiting complement activation will be administered to patients with GA. The goal of the study is to assess

the safety and tolerability of single dose IVT Fludrocortisone acetate. Results from this study will guide decisions to further develop intravitreal Fludrocortisone acetate for GA.

2.3.2 DOSE SELECTION

A single dose of 1mg/0.1mL or 2mg/0.1mL injection administered once will be tested in this study (see Section 5.2.1). Intravitreal fludrocortisone acetate was well-tolerated in a panel of animal toxicology studies. The volume of the human vitreous is approximately 4 mL, which is approximately 2.7-fold larger than the mean vitreous volume of rabbits, 1.5mL. Based on the difference in vitreous volume between man and rabbit, the human equivalent dose was determined to be 67 mg/eye every 4 weeks. The dose (1- or 2mg/0.1 mL injection) of Fludrocortisone acetate that will be evaluated in this clinical study is expected to result in drug concentrations approximately 1.3 fold lower than observed in rabbits.

2.3.3 RISK/BENEFIT

The safety monitoring practices employed by this protocol (e.g. complete ophthalmologic exam, IOP monitoring, OCT, vital signs, hematology, serum chemistry, and AE questioning) are adequate to protect the subjects' safety.

There are risks associated with the ophthalmic procedures required for participants in this study. However, these are all standard procedures that are widely performed in ophthalmology.

In the days following any IVT injection, patients are at risk of developing endophthalmitis. If the eye should become red, sensitive to light, painful, or develop a change in vision, the patient will be instructed to seek immediate care from an ophthalmologist. Other risks of IVT injection include traumatic cataract, retinal detachment and hemorrhage.

Transient increased IOP has also been identified as a risk following IVT injections. IOP will be carefully monitored in this study.

The approximately 150 mL of blood (See Section 9.9) planned for collection from each subject over the 6 months of the study does not pose an undue risk in this patient population.

Based on data available to date, IVT administration of Fludrocortisone acetate does not seem to present an unreasonable ophthalmic or systemic risk in animal models. Fludrocortisone acetate has been safely used systemically as mineralocorticoid replacement for severe orthostatic hypotension in Addison's disease and other salt-water disbalances.

However, as Fludrocortisone acetate has not been used intravitreally in human participants there are potential unforeseen risks. To mitigate such risks, this study is being conducted in two parts, restricting treatment to a single individual together with extended assessment, prior to application in other participants. Numerous follow-up visits and numbers of testing procedures have also been instituted in the assessment schedule for all participants to ensure adverse events, or other safety issues that arise are identified and addressed in a timely manner.

There is a potential health benefit for trial participants from receipt of study drug. We propose to administer intravitreal Fludrocortisone acetate to patients with GA. If efficacious, intravitreal Fludrocortisone acetate is expected to alter the course of GA and slow its rate of progression.

3 OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

The primary objectives of the study are to assess the safety and tolerability of IVT injections of Fludrocortisone acetate in subjects with GA associated with Age-Related Macular Degeneration in order to support further development into confirmatory Phase II studies.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY SAFETY ENDPOINT

To demonstrate safety and tolerability of IVT injections of Fludrocortisone acetate based upon the mean change in GA lesion size as measured by Fundus Autofluorescence (FAF).

- Number and severity of local and systemic treatment emergent adverse events.
-

3.2.2 SECONDARY ENDPOINTS

- The change in square root geographic atrophy (GA) lesion size from baseline to Month 6 as measured by FAF.
- Change in best corrected visual acuity (BCVA).
- Change in low luminance best corrected visual acuity (LL-BCVA).
- Relationship between GA lesion size changes and changes in BCVA.
- Change in vital signs.

- Increase in intraocular pressure (IOP).

Pharmacokinetic (PK) parameters

- Exposure after single dose Fludrocortisone acetate IVT injections.
- Serum maximum observed concentration.
- Time to maximum measured concentration
- Terminal elimination half-life.

4 STUDY POPULATION

The study population includes approximately 9 (n=9) subjects to be enrolled at approximately 1 site. To participate in the study, subjects must be diagnosed with GA of the macula associated with AMD in both eyes. If both eyes meet the criteria and qualify for the study, the eye with the best visual acuity at the screening visit will be designated as the study eye. If both eyes have the same visual acuity, the right eye will be used as the study eye.

The complete inclusion and exclusion criteria are presented in the Synopsis, Section 1.

4.1 WOMEN OF CHILDBEARING POTENTIAL

WOCBP are defined as pre-menopausal women physiologically capable of becoming pregnant.

4.2 WOMEN OF NON-CHILDBEARING POTENTIAL

WONCBP are defined as women meeting any of the following criteria:

• Older than 45 years with amenorrhea for > 2 years or older than 60 years with amenorrhea for > 1 year. Both confirmed by FSH and LH levels.

• Has undergone hysterectomy,

• Has undergone bilateral oophorectomy,

• Has undergone bilateral salpingectomy

4.3 APPROVED METHODS OF CONTRACEPTION

Approved methods of contraception include: oral contraceptives, intrauterine device, medically acceptable barrier methods (i.e. condom), implantable or injectable contraceptives or removable birth control device. Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an approved method of contraception during the study

5 TREATMENT OF SUBJECTS

5.1 ALLOCATION OF TREATMENT

Each subject will be assigned a unique screening number before screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be scheduled to enter the study and will receive treatment with intravitreal Fludrocortisone acetate on Day 0.

5.2 TREATMENTS ADMINISTERED

5.2.1 DOSE LEVELS AND STUDY ARMS

A single dose of 1- and 2 mg Fludrocortisone acetate/0.1mL will be tested in this study. Subjects will receive 1 IVT injection as outlined in the table below.

	Treatment Arm	Dose Escalation
Part 1	Fludrocortisone acetate 1 mg/0.1mL at Day 0	If no dose limiting toxicity is observed in 3 patients at this given dose level, the dose will be escalated to the following level:
Part 2	Fludrocortisone acetate 2 mg/0.1mL at Day 0	

5.2.2 DRUG SUPPLIES

5.2.2.1 IDENTITY OF INVESTIGATIONAL PRODUCT

Fludrocortisone acetate is formulated for intravitreal administration as a 20mg powder for solution for injection.

Each vial contains 10mg of fludrocortisone powder. The diluent consists of Carboxymethylcellulose (0.6%), Polysorbate 80 (0.02%) and Sodium Chloride solution (0.9%) quantity sufficient to 100%. The fludrocortisone powder for solution for intravitreal injection is reconstituted with 1.0ml and 0.5ml diluent for injection dependent upon concentration required. Following reconstitution, the concentration is suitable for delivering at a 1mg/0.1ml or 2mg/0.1ml dose in 0.1 ml intravitreal injection volume.

The fludrocortisone acetate 10mg powder for solution and diluent is for single use and must be stored at 2-8°C, protected from light.

5.2.2.2 ACCOUNTABILITY

IVT Fludrocortisone acetate drug product will be provided to a designee at the study site and must be stored in a pharmacy or otherwise locked and secured, at temperatures between 2°C and 8°C in a refrigerated area with limited, controlled access and temperature monitoring; do not freeze. IVT Fludrocortisone acetate drug should be protected from light by storing in the carton provided. The drug product supply is accessible only to those individuals authorized by the PI. The Sponsor will supply sufficient quantities of Fludrocortisone acetate drug product to allow completion of this study.

Designated study staff will provide the study treatments to the subjects in accordance with their assigned subject numbers and the randomization schedule. During the study, the receipt of the drugs supplied at the clinical site and of study treatment dispensation for each subject will be documented in drug accountability records. These drug accountability records are to be kept separate from the patient medical records and other source documents.

All used vials should be retained by the clinical site until drug accountability monitoring is performed and then returned to the Sponsor or designee, or destroyed per Sponsor instructions.

At the conclusion of the study, any unused investigational product will be retained by the clinical site, returned to the Sponsor or designee, or destroyed per Sponsor instructions, and this will be documented in the drug accountability records.

5.2.3 INTRAVITREAL FLUDROCORTISONE ACETATE ADMINISTRATION

Subjects receiving active treatment will be administered a 1mg/0.1ml or 2mg/0.1mL IVT injection of Fludrocortisone acetate using a 27G thin wall needle, at the discretion of the PI.

Clinic staff involved in the injection tray assembly, anaesthetic preparation, and study drug preparation and administration will follow appropriate aseptic techniques to minimize the risk of potential adverse events associated with IVT injections (e.g. endophthalmitis).

The investigation drug will be presented in a kit containing 1 x 1 ml syringe with 27g 12 mm needle, 1 x 5 ml vial containing sterile fludrocortisone 10mg, 1 x Vial containing 2 ml Diluent for reconstitution and alcohol swab to swab top of vials before puncturing bungs.

- Preparation of the solution
  The injecting doctor will withdraw 1.0ml or 0.5ml of diluent and reconstitute the powder. The doctor will then draw up 0.1 ml of the fluid ready for injection.

To minimize IOP elevation after IVT injection of Fludrocortisone acetate, decompression of the eye must be performed before all Fludrocortisone acetate injections. This is done by applying moderate pressure to the globe with cotton swabs for 30-60 seconds during aesthetic preparation.

In addition to the procedures outlined in this protocol, adherence to specific institutional policies associated with IVT injections will be observed.

5.3 CONCOMITANT THERAPIES

Any concomitant medications a participant is receiving at the start of the study or that are given for any reason during the study (except for routine medications given for

ocular procedures required by the protocol, such as topical aesthetic) must be recorded in the source document and CRF including start and stop date and time, dose, route, and indication. In addition, all ocular and non-ocular procedures such as surgical procedures (excluding study treatment procedures) must also be recorded in the source document including start and stop dates. Surgical anaesthetics, paramedical or alternative therapies (e.g. acupuncture, massage) should also be recorded in the source documents and CRF. Metoclopramide or other agents to prevent nausea induced by fluorescein injection may be administered at the discretion of the PI.

5.3.1 ENDOPHTHALMITIS TREATMENT

The decision to treat a participant for endophthalmitis or suspected endophthalmitis will be guided by the clinical judgment of the PI. The treatment method (pars plana vitrectomy vs. vitreous tap) and choice of antimicrobial agents are also at the discretion of the PI and should follow current standard practice patterns. The decision to use IVT steroids (e.g. dexamethasone) for the treatment of endophthalmitis is also at the discretion of the PI.

6 STUDY PROCEDURES

6.1 STUDY DESIGN

This is a Phase Ib study to assess the safety and tolerability of a single dose of IVT injection of Fludrocortisone acetate in subjects with GA associated with Age-Related Macular Degeneration.

Patients diagnosed with GA associated with age-related macular degeneration in the study eye and who meet all inclusion/exclusion criteria will be included in the study.

The study is planned to enroll an initial cohort of 3 patients in a dose of 1mg/0.1mL. A total of 9 participants can be included to assess dose escalation based on 3+3 algorithm.

Patients should be screened up to 14 days before receiving Fludrocortisone acetate. Upon entry into the study, patients will be assigned a subject screening number. Subjects who meet all inclusion and exclusion criteria and are confirmed as eligible by the CRC will return to the clinic for the administration of single dose IVT Fludrocortisone acetate (Day 0) as outlined in Section 7.1.

All subjects will return to the clinical site on Day 1 and Day 7 to assess acute safety after the injection. After that, all subjects will return for another 6 follow-up visits and 6 months after the injection. See Study Outline below.

Safety will be assessed throughout the study; serial blood samples and urine samples will be collected. Blood samples will also be collected for the PK assessment of Fludrocortisone acetate.

The planned length of participation in the study for each subject is approximately 6 months (from Day 0 – through completion of the Month 6 (Day 150) follow-up procedures).

The study is planned to take place over approximately 12 months (from screening of the first subject through completion of the last subject's exit visit).

6.2 SUBJECT ENROLLMENT

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study. Documentation of the personally signed and dated informed consent of each subject, using the study-specific ICF, is required before initiating the Screening process. After written informed consent has been obtained and eligibility to participate established, investigative site personnel will obtain the subject's identification number. Only eligible subjects will be allocated to the open label FCA 1 mg/0.1mL or 2mg/0.1 mL.

Enrollment will occur in two parts in order in order to minimise the likelihood that subjects will be exposed to risks. During part 1 & 2, subjects will be screened one by one as only one patient will initially be enrolled during part 1 of the trial. The first enrolled subject will participate in a screening period of up to 14 days and a follow-up period of 28 days, to detect an IOP response.

After first subject has completed the follow-up of 28 days after FCA 1mg/0.1 mL injection, The subject's safety data will be reviewed the safety data of this will be reviewed by an independent safety review committee to determine whether to commence enrolment of additional 2 patients in the first cohort of 1mg/0.1mL dose of FCA. Enrolment will be stopped if >2 patients experience limiting-toxicity adverse event related to the study drug. If no more than two adverse events considered to be related to the study drug occur with limiting toxicity, the second cohort will be recruited. Dose-limiting toxicity is defined by intraocular inflammation, elevated IOP, reduced vision (loss of ≥15 letters), or haemorrhage within 28 days after injection.

Part 2 will take in place if the 3 subjects have tolerated well the dose. Part 2 initially involves a single subject treated with 2mg/0.1mL FCA to assess safety and tolerability. This subject will be followed for up to 28 days and reviewed by an independent safety

review committee prior to the recruitment of a further 5 subjects treated with 2mg/0.1mL FCA totalling in 6 subjects in the second cohort.

Meeting minutes will be generated at each meeting and included in the sponsor's study files. Formal reports will not be prepared prior to or following these meetings. As general guidance, a subject will be considered to have tolerated a dose if the subject experiences no clinically significant drug-related adverse event or laboratory abnormality. Conversely, a subject will not be considered to have tolerated the dose if he experiences a clinically significant drug-related adverse event or laboratory abnormality during the study drug administration or post-administration follow-up period.

Safety to cataract will be reviewed among all participants at the 150 day review.

It is understood that safety is a medical judgment that cannot be prospectively defined in detail. Subjects will be closely monitored with clinical observations and safety laboratory testing.

6.3 STUDY VISIT SCHEDULE

Below is a condensed description of the study visits and the procedures and examinations that will be performed. Please refer to the Schedule of Activities (SoA) table in Section 1.2 for a detailed schedule of procedures/assessments for the Monthly visit schedules. Additional safety assessments not listed in section 8.3 or the flow chart may be performed if considered necessary at the discretion of the PI.

6.3.1 SCREENING – WITHIN 14 DAYS PRIOR TO TREATMENT

Visit 1 – All Subjects

All ophthalmic procedures (including imaging) are to be performed on both eyes:

1. Before any study specific procedures are performed, explain the purpose and nature of the study, and have the patient read, sign, and date the Institutional

Review Board/Independent Ethics Committee (IRB/IEC) - approved Informed Consent Form (ICF). Have the individual obtaining consent from the patient and a witness, if applicable, sign and date the ICF.

2. Obtain a screening number for the subject.
3. Obtain information on demographics, medical/ocular history, and concomitant medications used 90 days prior to enrollment. Include vitamins, and all over-the-counter as well as prescription medications.
4. Screen the patient for inclusion/exclusion criteria.
5. Collect blood (including blood for HCG/FSH/LH, if applicable) and urine for laboratory analysis and forward the samples to the central laboratory.
6. Collect vital signs.
7. Perform BCVA.
8. Perform LL-BCVA.
9. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
10. Perform SD-OCT imaging for determination of eligibility by the PI.
11. Perform FAF imaging for determination of eligibility by the PI.
12. Perform NIFR imaging.
13. Perform DCFP for determination of eligibility by the PI.
14. Perform FA for determination of eligibility by the PI.

6.3.2 Visit 2 (Baseline) – All subjects

Unless specified, all ophthalmic procedures (including imaging) are to be performed on the **Study eye only.**

1. Verify that all inclusion/exclusion criteria are met, including the determination of eligibility by the PI.
2. Obtain information on any changes in medical health and/or the use of concomitant medications.
3. Collect vital signs pre- and post-dose. Vital signs will be measured within 1 hour prior to dosing for the pre-dose time point. Post-dose vital signs readings will be performed within 30 minutes after dosing.
4. Perform BCVA.
5. Perform LL-BCVA.
6. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
7. Perform the IVT injection of fludrocortisone acetate.
8. Monitor the study eye within 15 minutes' post injection.
9. Monitor for adverse events.

6.3.3 Visit 3 (Day 1) – All Subjects. Post-initial treatment examination

Unless specified, all ophthalmic procedures (including imaging) are to be performed on the **study eye only.**

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Collect vital signs.
3. Perform BCVA.
4. Perform LL-BCVA.

5. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
6. Monitor for adverse events

6.3.4 Follow-up Visits – Day 7, 14, 28, 60, 90

Unless specified, all ophthalmic procedures (including imaging) are to be performed on the **study eye only.** The following procedures will be performed at all follow-up visits:

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Collect vital signs.
3. Collect blood for PK analysis (days 7, 28 and 90 only).
4. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
5. Monitor for adverse events

6.3.5 Termination Visit (or Early Termination) – Day 150

All ophthalmic procedures are to be performed on BOTH EYES.

1. Obtain information on any changes in medical health and/or the use of concomitant medications.
2. Collect blood and urine for laboratory analysis and forward the samples to the central laboratory.
3. Collect blood for PK analysis.
4. Collect vital signs.
5. Perform urine pregnancy test. -WOCBP only.
6. Perform BCVA.

7. Perform a complete ophthalmic exam including slit-lamp exam of the cornea, iris, anterior chamber, lens (LOCS III if any opacity on the lens noted) and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina and IOP measurement.
7. Perform SD-OCT imaging.
8. Perform FAF imaging.
9. Perform NIFR imaging.
10. Perform DCFP.
11. Perform FA imaging.
12. Monitor for adverse events

6.3.6 Unscheduled Visit

If a subject return to the clinical site before their next scheduled visit for an assessment of an adverse event or at the request of the PI, all assessments completed at the Unscheduled Visit should be documented in the patient source record and in the eCRF.

6.4 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for ≥1 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

7 STUDY ASSESSMENTS AND PROCEDURES

The following evaluations will be performed during the study outlined in the Schedule of Activities in Section 1.2.

7.1 INFORMED CONSENT PROCEDURES

The Principal Investigator(s) at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

7.2 VITAL SIGNS

On injection visit, vital signs will be measured within 1 hour prior to dosing and within 30 minutes after dosing.

Vital signs will be measured before venipuncture. Vital signs include blood pressure (BP) and pulse measurements. After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If vital signs are out-of-range at screening/eligibility, the Investigator may obtain two additional readings, so that a total of up to three consecutive assessments are made, with the patient seated quietly for approximately five minutes preceding each repeat assessment. At least the last reading must be within the ranges provided above in order for the patient to qualify. All of the above tests will be performed after resting for 3 minutes at all visits.

Height in centimetres (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Visit 1 (Screening). Body mass index (BMI) will be calculated using the following formula: BMI = Body weight (kg) / [Height (m)]^2.

7.3 LABORATORY ANALYSIS OF BLOOD AND URINE

Collection of blood and urine will occur at the study site and the samples will be shipped to a central laboratory for analysis.

The following clinical labs will be performed:

Hematology

• Hemoglobin

• Hematocrit

• Red blood cell (RBC) count

• Platelet count

• White blood cell (WBC) count with differential

Chemistry

• Blood urea nitrogen (BUN)

• Creatinine

• Bilirubin (total, direct and indirect)

• Albumin

• Alkaline phosphatase

(ALP)

• Aspartate aminotransferase (AST)

• Alanine aminotransferase (ALT)

• Creatine kinase

• Glucose

• Electrolytes (sodium, potassium, chloride, bicarbonate)

Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte esterase

Other

- Human chorionic gonadotropin (HCG) [a]
- Follicle-stimulating hormone (FSH) [b]
- Luteinizing hormone (LH) [b]

The Investigator must review the results of the Screening Visit clinical laboratory tests (including recheck results) and confirm that these results do not show evidence of any medical condition that would make study participation inappropriate. The Investigator should also assess any changes from baseline at the follow up visits and the Exit Visit.

Notes:

- a. Serum Pregnancy Test (i.e. HCG) will be performed for females of child bearing potential at screening only.
- b. FSH and LH will be performed for postmenopausal females at screening only.

7.4 URINE PREGNANCY TEST

Urine pregnancy test will be performed in WOCBP only as outlined in the Study Flow Chart in Section 1.2.

7.5 BEST-CORRECTED VISUAL ACUITY

Best-corrected visual acuity (including LL-BCVA) testing, performed by a certified VA examiner, should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. ETDRS best-corrected visual acuity (BCVA) will be obtained in each eye separately at screening (Visit 1). This assessment is to be performed prior to pupil dilation. The number of letters read correctly (for each eye) will be recorded in the appropriate study document. For the remainder of study visits (Visits 2-8), BCVA will only be obtained in the study eye.

7.6 COMPLETE OPHTHALMIC EXAM

The complete ophthalmic exam will consist of the following:

- External examination of the eye and adnexa.
- Routine screening for eyelids/pupil responsiveness (including ptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light and afferent pupillary defect).
- Slit-lamp examination [cornea, anterior chamber, iris, lens, aqueous reaction (cells and flare). If an abnormal lens finding is noted during the slit-lamp examination, at any visit, then the finding should be further characterized with LOCS III. All subsequent visits for that subject should include LOCS III. A

complete description of LOCS III standardized procedures and grading scales is outlined in the MOP.

- Dilated fundus exam including evaluation of retina and vitreous (i.e. posterior segment abnormalities, retinal hemorrhage/detachment, and vitreal hemorrhage density and vitreous cells).
- Vitreal hemorrhage density and vitreous cells grading scales.
- Intraocular pressure (IOP) will be measured in both eyes at Visit 1 as per the study site's regular practice and recorded in the appropriate study document. For the remainder of study visits (Visits 2-9), IOP will only be obtained in the study eye.

7.7 OCULAR IMAGING

The following ocular images will be obtained as outlined in the visit schedule in Section 6.3. Also see Study Flow Charts in Section 1.2.

- Digital Color Fundus Photographs
- Fluorescein angiography
- Spectral Domain Optical coherence tomography
- Fundus Autofluorescence
- Infrared reflectance imaging. Only done at selected clinical sites with Heidelberg Spectralis® system.
-

7.8 POST-INJECTION ASSESSMENT

The study eye will be assessed before and after injection to ensure that the injection procedure and/or the study medication have not endangered the health of the eye. The initial post-injection assessment should be done within 15 minutes' post-injection and

include a gross assessment of vision (light perception) and monitoring IOP. If subject passes gross vision test and IOP is < 30mmHg, the subject may leave the site. If subject fails gross vision test and/or IOP is > 30 mmHg, assessments will continue every approximately 30 minutes until the subject passes gross vision test and IOP is < 30 mmHg.

Any subject who develops a significant and sustained raise in IOP (> 30 mmHg) or a non-adequately perfused central retinal artery (CRA) after injection, should be monitored according to the PI's clinical judgment and may undergo additional procedures and measurements of IOP beyond those specified in the protocol as well as IOP lowering procedures. If any concern or immediate toxicity is noted, the subject will remain at the site and will be treated according to the PI's clinical judgment.

7.9 BLOOD VOLUME FOR STUDY ASSESSMENTS

Blood volume during study (up to Day 150)

Assay	Number of Time Points	Approximate Volume per Time Point (mL)	Approximate Sample Volume Over Course of Study (mL)
Pharmacokinetics	4/9	4	36
Haematology	5/9	4	36
Chemistry (Incl. HCG/LH/FSH)	5/9	8.5	76.5

Total Blood Volume for Study 148.5 mL

7.10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All adverse events (AEs) (as defined in Section 7.9.1), either observed by the PI or one of their medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported. All adverse events (ocular, non-ocular, serious, non-serious, volunteered, and elicited) must be documented in study records.

7.10.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any untoward medical occurrence in a subject who receives a pharmaceutical product. The occurrence does not necessarily have to have a causal relationship with the treatment. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug.

Note:

• For purposes of this study, abnormal laboratory values will not be considered adverse events unless deemed clinically significant by the Investigator. All abnormal laboratory values will be recorded in the database and appropriate analyses presented in the final study report.

7.10.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;

- Is life-threatening: this means that the subject was at risk of death at the time of the event; it does not mean that the event might have caused death had it occurred in a more severe form;
- Required hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- Is a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate

7.10.3 ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest is one of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. These adverse events may be serious or non-serious. Applicable adverse events may require further investigation in order to characterize and understand, and depending upon the nature of the event, rapid communication by the trial Sponsor to other parties may also be required. These adverse events of special interest must be reported using the same mechanism and timeframe (i.e. within one working day of the Investigator's or delegate's knowledge of the event) as described for serious adverse events in Section 7.9.2. The adverse events of special interest include the following:

- Endophthalmitis
- 4+ ocular inflammation

- 2-3+ ocular inflammation that fails to decrease to 1+ or less within 30 days of the onset of the event
- Sustained (> 5 minutes) loss of light perception after FCA injection
- Sustained elevation of IOP (30 mmHg) at/past 90 minutes' post-injection
- Any elevation of IOP requiring surgical intervention (i.e. paracentesis)
- New vitreous hemorrhage of > 2+ severity that does not resolve within 14 days of the onset of the even
- Cataract progression

If an adverse event of special interest occurs in a study subject, the study subject will be followed for resolution of the adverse event. A decision will be made by the Sponsor concerning further exposure to the study treatment and further participation in the study.

7.10.4 ADVERSE EVENT ASSESSMENT AND RECORDING

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. For each AE, the PI should note the start and resolution dates, the severity, whether it meets the definition of an SAE (see Section 7.9.2), the relationship of the event to the study drug, the action taken regarding study drug, and the outcome of the event. Data should be transcribed from the source documents to the CRF as per the CRF instructions.

When reporting an adverse event, the event description should use the best matching terminology describing the event as found in the "Common Terminology Criteria for Adverse Events" (CTCAE, v 4.03). If an available CTCAE term fits the event well, no additional descriptors may be needed.

However, the Investigator should add any necessary descriptions in order to clarify the event or to place it in an appropriate context. If an appropriate term matching the adverse event cannot be found in the CTCAE and you do not know the preferred MedDRA term, the adverse event description should include a diagnosis, sign or

symptom with additional information to facilitate subsequent categorization into MedDRA coding terms

7.10.4.1 INTENSITY

The PI must grade the severity of all reported adverse events into one of five categories: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening) or Grade 5 (Death related to AE). The standardized CTCAE severity grading scales for the specific type of adverse event reported must be used when a matching CTCAE term is available. If no reference to a standard grading scale applies or is immediately available, use the following guideline:

7.10.4.1.1 GRADE 1 –MILD

Persistence of any otherwise insignificant medical occurrence beyond 72 hours or any transient (< 72 hours) AE considered by the PI to be related to the study drug. No or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities; nonprescription or single-use prescription therapy may be employed to relieve symptoms. Mild adverse events may be listed as expected consequences of the therapy for any given protocol, and standard supportive measures for such an expected event do not necessarily elevate the event to a higher grade.

7.10.4.1.2 GRADE 2- MODERATE

Mild to moderate limitation in activity, some assistance may be needed; possibly none but usually minimal intervention/therapy required, hospitalization possible.

7.10.4.1.3 GRADE 3- SEVERE

Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely. [Specifically, for ocular adverse events in this vision related study, an immediately sight-threatening condition (e.g., impending corneal perforation, retinal detachment) may be categorized as Grade 3 if it would lead to total blindness in the affected eye(s).]

7.10.4.1.4 GRADE 4- LIFE THREATENING

Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment or hospice care probable. This grade is used when the participant was, in the view of the PI, at substantial risk of dying at the time of the adverse event or it was suspected that use or continued use of the test article would have resulted in the participant's death. (This does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.)

7.10.4.1.5 GRADE 5- DEATH

Death related to AE

7.10.4.2 CAUSALITY

The PI (or an authorized study physician) must submit an attribution for causality of the reported adverse event to the test article or procedure.

The attribution should take into account both the temporal association and any known physical, physiological or toxicological information regarding the test article that could reasonably infer causality. Causality should only be considered for the experimental test article and not for any standard study examination or diagnostic procedures. The four attribution categories are:

Unrelated	Does not follow a reasonable temporal sequence from the administration of study drug. The event or laboratory test abnormality is clearly due to extraneous causes (disease, other drugs, environment, etc.)
Unlikely related	Does not follow a known pattern of response to study drug. Does not follow a reasonable temporal sequence from the administration of study drug. Disease or other drugs provides plausible explanation. It does not reappear or worsen when study drug is re-administered
Possibly related	Follows a known pattern of response to study drug. Time sequence from administration of the study drug is reasonable. Could also be explained by disease or other drugs.
Probably related	Follows a known pattern of response to study drug. Time sequence from administration of the study drug is reasonable. Response to withdrawal clinically reasonable. Cannot be reasonably explained by the known characteristics of the participant's clinical state, environmental factors, or other therapies administered to the subject

7.10.5 SERIOUS ADVERSE EVENT REPORTING

All SAEs (defined in Section 7.9.2), whether judged related or not to study medication, will be reported to the Sponsor (or designated Medical Monitor) by telephone, e-mail or facsimile within 24 hours of the Investigator becoming aware of such SAEs. The contact details can be found of the serious adverse event form.

The initial SAE Report should include, at a minimum, the following information:

- Protocol number
- Site number
- Subject screening number, initials, gender, and date of birth
- Name of PI and investigator site address
- Details of SAE
- Criterion for classification as “serious”
- Date of SAE onset

Follow-up SAE reports should be submitted as further information becomes available, and the final SAE Report should include information on the SAE intensity, outcome, and relationship to study drug; dates of study drug administration, concomitant medications, and any other relevant information. The PI should also provide clear copies of supporting documents as necessary (e.g. hospital discharge summary, laboratory reports, autopsy reports, etc.), with the subject’s personal identifiers removed. All SAEs will be followed until the acute event has resolved, even if the subject discontinues study participation prior to the resolution. The Investigator must report SAEs occurring at his/her site to the IRB/IEC as required.

7.11 EXPECTED ADVERSE EVENTS

7.11.1 EXPECTED AE RELATED TO THE TEST ARTICLE

No ocular or systemic AE related to the investigational drug are expected at the doses proposed in this protocol.

7.11.2 EXPECTED AE RELATED TO THE IVT INJECTION PROCEDURE

Mild discomfort related to the injection procedure (including use of an eyelid speculum, anaesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush and subconjunctival injection of anaesthetic, as well as the actual insertion of the IVT needle) are expected. These procedure-related adverse events include but are not limited to: redness, mild eye pain, eye irritation, visual disturbance, abnormal sensation in the eye, etc. and will be graded as indicated in Section 7.9.4.

7.11.3 DISEASE PROGRESSION

A condition considered by the PI as unequivocal AMD disease progression in the study eye or fellow eye should be identified as such in the participant's source documents and should not be recorded as an adverse event in the CRF, such as lesion growth, lesion bleeding, lesion that exudes fluid, an RPE tear, and extensive deposition of lipid. All other conditions should be recorded as an adverse event. The unequivocal nature of the disease progression must be indicated in the source documents. Normal progression or worsening of the medical condition under study (e.g. vision loss due to the progression of AMD), by itself, does not necessarily constitute an adverse event unless the change

can be reasonably attributed to an action of the test article and not only to its lack of efficacy.

7.11.3.1 WITHDRAWAL

Participants may choose to withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other clinical protocols.

Participant wishing to withdraw from the study completely will be offered an early termination visit.

This early termination visit will include the examinations outlined in Section 6.3.1.

7.11.4 PREGNANCY IN THE CLINICAL TRIAL

Women of childbearing potential (WOCBP) are not excluded from the study as long as adequate birth control methods are being utilized. Prior to enrollment in the clinical trial, WOCBP must be advised of the importance of avoiding pregnancy during the trial and the potential risks associated with an unintentional pregnancy. WOCBP and males with partners who are WOCBP will be instructed to practice an acceptable method of birth control (as defined in Section 4.3) for the duration of the study. Male subjects will be counselled to avoid donating sperm after dosing on Day 1 until the final Exit visit.

During the trial, female subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. The study Sponsor must be contacted immediately and a decision will be made regarding continuation of the pregnant woman in the study based upon the circumstances surrounding the pregnancy. Pregnancy is not reportable as an adverse event; however, complications may be reportable. If a female subject or partner of a male subject becomes pregnant during the study, the PI should report the pregnancy to the Medical Monitor within 24 hours of being notified. The Investigator should follow the pregnancy until completion. At

the completion of the pregnancy, the Investigator will document and report the outcome. If the outcome of the pregnancy meets the criteria for classification as an SAE (i.e. postpartum complication, stillbirth, neonatal death, or congenital anomaly) the Investigator should follow the procedures for reporting an SAE.

8 STATISTICAL CONSIDERATIONS

Descriptive summaries will include mean, standard deviation, median, and range for continuous variables and counts and percentages for categorical variables.

8.1 POPULATION FOR ANALYSIS

- Safety Analysis:

All subjects who received at least one dose of treatment will be included in the evaluation of safety of FCA.

- Efficacy Endpoint(s):

The efficacy analysis will be based on an intention-to-treat population (ITT), which is defined as all subjects who received the single dose of treatment and have at least one visit at or after month 2. Month 2 is the first visit on treatment at which lesion area is measured. Per protocol (PP) efficacy analyses will include all randomized subjects who return for Day 150 of follow up.

Safety is the main analysis population for safety endpoints, and ITT is the main analysis population for efficacy endpoints. The assignment of participants to each analysis population will be based on the review of data after the completion of all data collection, monitoring by the clinical research associate and first round of query resolution by data management and prior to database lock.

8.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Participant demographic and baseline variables (age, sex, ethnicity, race, height, weight, and BMI) will be summarised with descriptive statistics. Sex, ethnicity, and race will be summarised with frequency counts and percentages. Baseline ocular assessments will be summarised descriptively as well.

Pregnancy test results, concomitant medication and medical history data for each participant will be presented in data listings. Concomitant medications will be summarised descriptively by using frequency counts and percentages.

8.3 ANALYSIS OF PRIMARY SAFETY ENDPOINTS

No formal inferential statistics will be performed on safety assessments. Statistical methods for the safety analyses will be primarily descriptive in nature. The Fludrocortisone acetate 1mg/0.1mL and 2mg/0.1 mL injection will be considered as safe and tolerable based on the number of subjects presenting severe AEs related to the study drug. It is understood that safety is a medical judgment that cannot be prospectively defined in detail. However, as general guidance, a subject will be considered to have tolerated a dose if the subject experiences no clinically significant drug-related adverse event or laboratory abnormality. Conversely, a subject will not be considered to have tolerated the dose if he experiences a clinically significant drug-related adverse event or laboratory abnormality during the study drug administration or post-administration follow-up period.

Listings and summaries for all safety data will be presented using the Safety Population. Descriptive statistics (mean, SD, median, minimum and maximum) will be calculated for summaries of continuous safety data and frequency counts and percentages (where appropriate) will be calculated for summaries of discrete/categorical safety data.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and data will be summarised by System, Organ, Class and preferred term. The number and percent of participants reporting each AE will be summarised descriptively (n=9). A participant with two or more AEs within the same level of summarisation (i.e., system, organ, class or preferred term) will be counted only once in that level. The number of AEs reported will also be presented. Adverse events will also be summarised by severity as well as relationship to study treatment. A by-participant AE data listing, including verbatim term, preferred term, system organ class, severity, and relationship to study treatment, will be provided. Separate listings will be generated for SAEs and AEs leading to study/treatment discontinuation.

All haematology, blood chemistry and urinalysis (continuous variables) parameters will be summarised using descriptive statistics for all study visits assessed, including change from baseline (last pre-surgery value) for all post-surgery assessments. All laboratory data will be included in the data listings and all test values outside the normal range will be flagged.

All vital sign parameters will be summarised using descriptive statistics by study visit, including change from baseline (last pre-surgery) for all post-surgery assessments.

Individual vital sign assessments will be listed for each participant. Findings of physical examinations will be listed for each participant and summarised descriptively by using count and percentage by study visit.

8.4 ANALYSIS OF SECONDARY ENDPOINTS

The efficacy endpoints are the secondary endpoints of this study, which include complete ocular examination.

ETDRS best-corrected visual acuity (BCVA) will be scored with reference to the Early Treatment Diabetic Retinopathy Study ETDRS letters). ETDRS will be treated as continuous data, and descriptive statistics (mean, SD, median, minimum and maximum) will be summarised for ETDRS observed value and change from baseline at each post-

surgery visit. Exploratory analysis of ETDRS change over time will be assessed by using a mixed model. The correlations between repeated measures of the same participant will be accounted for by the mixed model. The least squares mean of ETDRS change from baseline and its 95% confidence interval at each visit will be estimated. Similar analyses will be conducted for intraocular pressures. Categorical efficacy endpoints such as slit lamp biomicroscopy exam findings, dilated ophthalmoscopy exam findings, color fundus photography and OCT finding will be summarised descriptively by frequency count and percentage (proportion) where appropriate.

8.5 INTERIM ANALYSIS

There is no formal interim analysis planned for this study.

8.6 SAMPLE SIZE

The study is planned to enrol up to 12 participants with geographic atrophy secondary to age-related macular degeneration with visual acuity (20/32 to 20/2000, Snellen's equivalent), following the 3+3 method.

The sample size chosen for this study was selected without formal statistical justification, but the numbers chosen are considered adequate for assessing the study objectives. The sample size was determined on the basis of practical and logistical considerations and not based on statistical power with regard to hypothesis testing or precision with regard to parameter estimation.

This phase 1 trial was designed to identify any important limiting toxicities and to determine if this dose is suitable for phase 2 trial. This was also designed to minimize the likelihood that a minimum number of subjects will be exposed to the investigational drug.

This is an open label study, and no randomization is conducted in this study.

8.7 MISSING DATA

Missing data will generally not be imputed for safety or efficacy data.

9 DATA COLLECTION, RETNETION AND MONITORING

9.1 DATA COLLECTION INSTRUMENTS

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each participant treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Participants will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, participant number and initials.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. The Investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

9.2 DATA MANAGEMENT PROCEDURES

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

9.3 DATA QUALITY CONTROL AND REPORTING

After data have been entered into the study database, a system of computerised data validation checks will be implemented and applied to the database on a regular basis.

Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

9.4 ARCHIVAL DATA

The database is safeguarded against unauthorised access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

9.5 AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA, TGA) inspectors upon request. A file for each participant must be maintained that includes the signed informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

All study documents (patient files, signed informed consent forms, copies of eCRFs,

Study File Notebook, etc.) must be kept secured for a period of fifteen years following the completion of the study.

9.6 MONITORING

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

9.7 DATA SAFETY MONITORING BOARD

An independent DSMB will be convened. The mission of the DSMB will be to ensure the ethical conduct of the trial and to protect the safety interests of patients in this study. The DSMB will be responsible for reviewing the cumulative safety results from the study. The DSMB will meet prior to the commencement of the study, and will review all

available safety/tolerability data (e.g., adverse events, serious adverse events, clinical laboratory assessments, blood pressure, haematology, urology) at Day 0 and 1 month after IVT injection of FCA of the initial participant in Part 1 and 3 (prior to Part 2 & 4 of the study), and convene as required throughout the study period to review data and potential safety risks. The criteria for evaluating study continuation will relate to study safety, including the incidence and severity of ocular and/or systemic side effects not limited to but including; change in IOP of >10mmHg, a loss of 15 letters or more in BCVA, presence or intraocular inflammation, presence or absence of ocular pain, change in BP of 30mmHg (systolic or diastolic), incidence of hospitalisation or systemic illness, and any other ocular or systemic adverse events reported. Any changes will be referenced to baseline measurements. The DSMB will then meet at the conclusion of the study and after the final statistical analysis in order to review all data.

DSMB will consist an ophthalmologist, and a biostatistician, both independent of the study team.

9.8 PARTICIPANT CONFIDENTIALITY

In order to maintain participant confidentiality, only a site number, participant number and participant initials will identify all study participants on eCRFs and other documentation submitted to the Sponsor. Additional participant confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

10 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the TGA. The Investigator must also comply with all applicable privacy regulations (e.g*., The Health Records and Information Privacy Act 2002).*

10.1 PROTOCOL AMENDMENTS

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

10.2 INSTITUTIONAL REVIEW BOARDS AND INDEPENDENT ETHICS COMMITTEE

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating centre prior to study initiation. Serious adverse events regardless of

causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfil its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 INFORMED CONSENT FORM (ICF)

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25 [a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form (ICF) to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each participant prior to entering the participant into the trial. Information should be given in both oral and written form and participants (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the participant will also be obtained. If a participant is unable to sign the ICF and the HIPAA authorization, a legal representative may sign for the participant. A copy of the signed consent form (and assent) will be given to the participant or legal representative of the participant and the original will be maintained with the participant's records.

10.4 PUBLICATIONS

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among

the study Sponsor and participating institutions. In addition, upon study completion and finalization of the study report \the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 INVESTIGATOR RESPONSIBILITIES

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of participants.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.

8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to participants or others (to include amendments and IND safety reports).

9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/participants.

10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312

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