Document: Study Protocol and Statistical Analysis Plan

Protocol Number: OPT-302-1004

Official Title: [ShORe] A Phase 3, Multicentre, Double-masked, Randomised Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

NCT Number: NCT04757610

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ShORe

A Phase 3, Multicentre, Double-masked, Randomised Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

Protocol Number:	OPT-302-1004
EudraCT Number:	2020-004736-24
[redacted]	[redacted]
Investigational Product:	OPT-302, sozinibercept
Development Phase:	3
Sponsor:	Opthea 650 Chapel Street South Yarra, VIC 3141 Australia
Sponsors' Clinical Representative:	[redacted]
Medical Expert:	[redacted]

CONFIDENTIAL

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TABLE OF CONTENTS

Opthea Limited, 650 Chapel Street, South Yarra, VIC 3141, Australia

[redacted]

[redacted]

LIST OF TABLES

LIST OF FIGURES

Opthea Limited, 650 Chapel Street, South Yarra, VIC 3141, Australia

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

By signing this protocol, the Principal Investigator acknowledges and agrees:

The protocol contains all necessary details for conducting the study. The Principal Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice[1] (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study documentation within a timely manner. The Principal Investigator is responsible for the medical care of each study participant enrolled from the study site, and all study-related medical decisions.

The protocol and the Investigator's Brochure (IB)[2] containing all relevant information on the drug relating to pre-clinical and prior clinical experience will be made available to all physicians, nurses and other personnel who participate in the conduct of this study. The Principal Investigator will discuss this material with these individuals to assure that they are fully informed regarding the study drug(s) and the conduct of the study.

This document contains information that is privileged or confidential. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential and must agree to maintain confidentiality. These restrictions on disclosure will apply equally to all future information supplied that is indicated as privileged or confidential or which it is apparent from the context and subject matter is confidential in nature.

Opthea will have access to any source documents from which electronic Case Report Form (eCRF) information has been derived. The eCRFs and other data pertinent to this study are the property of Opthea and Opthea may utilise the data in various ways such as, for example, submission to government regulatory authorities, or in publication of the results of the study.

Site Principal Investigator Signature	Date

Site Principal Investigator Name	Site Name

LIST OF ABBREVIATIONS

[redacted]	[redacted]
ADR	Adverse Drug Reaction
AE	Adverse event / Adverse experience
[redacted]	[redacted]
AMD	Age-related Macular Degeneration
[redacted]	[redacted]
[redacted]	[redacted]
BCVA	Best-corrected Visual Acuity
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
cGMP	Current Good Manufacturing Practice
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted])
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
eCRF	Electronic Case Report Form
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ETDRS	Early Treatment Diabetic Retinopathy Study
[redacted]	[redacted]
FDA	Food and Drug Administration
FA	Fluorescein Angiography
[redacted]	[redacted]
GCP	Good Clinical Practice
[redacted]	[redacted]
GMP	Good Manufacturing Practice
[redacted]	[redacted]
HMA	Heads of Medicines Agencies
IB	Investigators' Brochure
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent or Institutional Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]l
IRB	Institutional Review Board
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IVT	Intravitreal
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MHRA	Medicines and Healthcare Products Regulatory Agency
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
N	Number (typically refers to participants)
[redacted]	[redacted]
NIH	National Institutes of Health (US)
[redacted]	[redacted]
OD	*Oculus Dextrus/Dexter* (right eye)
OS	*Oculus Sinister* (left eye)
OU	*Oculus Uterque* (both eyes)
[redacted]	[redacted]
[redacted]	[redacted]
PI	Principal Investigator
PIN	Participant Identification Number
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
REC	Research Ethics Committee
SAE	Serious Adverse Event
[redacted]	[redacted]
[redacted]	[redacted]
SIV	Site Initiation Visit
SOPs	Standard Operating Procedures
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
TEAE	Treatment-Emergent AE
[redacted]	[redacted]
[redacted]	[redacted]

VEGF	Vascular Endothelial Growth Factor
VEGFR	VEGF Receptor
UADR	Unexpected Adverse Drug Reaction
[redacted]	[redacted]
[redacted]	[redacted]

1. PROTOCOL SYNOPSIS

Study Title:	A Phase 3 study of intravitreal OPT-302 in combination with ranibizumab, compared with ranibizumab alone, in participants with neovascular age-related macular degeneration (AMD).
Study Name:	**ShORe** – Study of **O**PT-302 with **R**anibizumab in neovascular AMD
Development Phase:	Phase 3
Primary Objective:	To determine the efficacy of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 0.5 mg ranibizumab, in participants with neovascular AMD.
Secondary Objectives:	To determine the effects of the addition of intravitreal 2.0 mg OPT-302 to intravitreal 0.5 mg ranibizumab from Baseline to (and at) Week 52 in terms of: ***Efficacy:*** • Changes in Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) letter score [redacted]
Primary Endpoint:	• Mean change from Baseline to Week 52 in ETDRS BCVA letters
Secondary Endpoints:	***Efficacy:*** • Proportion of participants gaining 15 or more ETDRS BCVA letters from Baseline to Week 52 • Proportion of participants gaining 10 or more ETDRS BCVA letters from Baseline to Week 52 • Change in CNV area by fluorescein angiography (FA) from Baseline to Week 52 • Proportion of participants with absence of both SRF and IR cysts by spectral domain optical coherence tomography (SD-OCT) at Week 52 ***Safety:*** [redacted]
Safety and Tolerability Evaluations:	[redacted]

Study Design:	Phase 3, multicentre, randomised, parallel-group, sham-controlled, double-masked, superiority study
Investigational Product:	2.0 mg OPT-302 intravitreal injection
Co-administered anti-VEGF-A therapy:	0.5 mg ranibizumab intravitreal injection
Control:	Sham intravitreal injection
Study Arms:	Three study arms, randomised in a 1:1:1 ratio (see Figure 1-1): • ***Standard Dosing*** 2.0 mg OPT-302 (50 µl) intravitreal injection with 0.5 mg ranibizumab (50 µl) intravitreal injection, both administered 4-weekly (q4w). • ***Extended Dosing*** 2.0 mg OPT-302 (50 µl) intravitreal injection (3 doses at 4-weekly intervals, and then 8-weekly [q4w x 3 then q8w]) with sham injection at visits when OPT-302 is not administered, with 0.5 mg ranibizumab (50 µl) intravitreal injection 4-weekly (q4w). • ***Control*** Sham intravitreal injection with 0.5 mg ranibizumab (50 µl) intravitreal injection, both administered 4-weekly (q4w).
Treatment Regimen:	Efficacy Phase: Study treatment administered per randomised treatment group, commencing at the Baseline visit for a period of 48 weeks. The last dose prior to efficacy assessments at Week 52 will be administered at Week 48. Safety Phase: Continuing study treatment administered per randomised treatment group, commencing after all efficacy assessments have been completed at Week 52, for a period of 48 weeks to Week 96.
Masking:	The participant, BCVA examiners, assessing Clinical Investigators, and image graders from the Independent Reading Centre (IRC), will be masked to study treatment allocation.
Stratification:	[redacted]
Planned Sample Size:	Approximately 330 participants per treatment group, approximately 990 in total
Key Eligibility Criteria:	***Key Inclusion Criteria*** • Male or female participants at least 50 years of age. • Active subfoveal CNV lesion or juxtafoveal CNV lesion (1-199 µm from the fovea) with foveal involvement (demonstrated by leakage on FA and/or IR fluid or SRF on SD-OCT) that is secondary to AMD in the Study Eye. [redacted] • An ETDRS BCVA score between 60 and 25 (inclusive) letters in the Study Eye.

Key Exclusion Criteria

Study Eye:

- Any previous treatment for neovascular AMD, [redacted]
- [redacted]
- Clinically significant ocular disorders (other than neovascular AMD), which may, in the investigator's opinion, interfere with assessment of BCVA, assessment of safety, or fundus imaging.

[redacted]

Duration per Participant:	[redacted]
Study Procedures:	[redacted]
Study Restrictions:	[redacted]
Safety Monitoring:	[redacted]
Statistical Analyses:	[redacted]

[redacted]

2. INTRODUCTION

2.1 Background

Age-related macular degeneration (AMD) is a chronic degenerative eye disease of the central retina, that causes a progressive, irreversible, severe loss of central vision. In developed nations it is by far the leading cause of vision loss in both men and women.[3] In many countries, AMD leads to as many blind registrations than all other eye diseases combined. There are two main types of AMD: dry-AMD and neovascular AMD. Although neovascular AMD is less common, affecting only 10% of AMD patients, it is more likely to lead to significant vision loss and blindness. Neovascular AMD is associated with choroidal neovascularisation (CNV), in which new blood vessels from the choroid break through to the neural retina, leaking fluid, lipids and blood, and leading to fibrous scarring and loss of vision.[4] Visual deterioration associated with neovascular AMD can be rapid, generally severe, and significantly deteriorates patients' quality of life.[5]

Vascular endothelial growth factor A (VEGF-A) is a heparin-binding glycoprotein with potent angiogenic, mitogenic and vascular permeability-enhancing activities specific for endothelial cells.[6] Although the underlying aetiology of neovascular AMD is complex, it has been established that VEGF-A plays a pivotal role in the growth of the abnormal blood vessels (*ie.* CNV lesions), and therefore inhibiting VEGF-A has become a key target for effectively controlling neovascular AMD.[7] Currently four therapies that primarily target VEGF-A inhibition have been approved by global regulatory agencies for the treatment of neovascular AMD: pegaptanib, ranibizumab, aflibercept and recently brolucizumab (although pegaptanib is not often used in clinical practice).[8,9,10,11,12,13,14,15,16] Off-label use of bevacizumab (approved for use in oncology indications), an anti-VEGF-A therapy with similar properties to ranibizumab, has also become common.[17] These therapies have revolutionised the treatment for neovascular AMD over the last decade, where initial disease stabilisation with the first agent, pegaptanib,[18] was then exceeded by reversal of disease and significant vision gains with ranibizumab,[19,20,21] bevacizumab,[22] and aflibercept.[23]

Mean vision gains observed over 12-months in the pivotal studies for these anti-VEGF-A therapies ranged from +6.1 to +11.3 Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) letters. The MARINA study reported a gain of +6.5 to +7.2 letters,[20] ANCHOR +8.5 to +11.3,[21] VIEW (control groups) +8.1 to +9.4,[23] and CATT (control group) reported a gain of +8.5 with monthly ranibizumab.[22] The CATT study reported a gain of +8.0 letters with monthly bevacizumab.[22] The VIEW studies reported gains of +6.9 to +10.9 letters with 1-2 monthly aflibercept,[23] and the HAWK and HARRIER studies reported gains of +6.1 to +6.9 letters with 1-3 monthly brolucizumab. [24]

Despite these significant gains or stabilisation of vision, at least 45% of patients with neovascular AMD exhibit some degree of resistance (characterised by failure to gain or maintain vision) to therapies that selectively target VEGF-A.[25,26] Newer agents have focussed on non-inferiority to existing anti-VEGF-A therapies with extended treatment intervals, rather than providing superior vision gains.[24] It is thought that treatment resistance occurs as selective VEGF-A inhibitors do not fully address the multifactorial pathogenesis of CNV formation.[27,28] Combination therapy targeting alternative mediators of neovascular disease progression, is expected to play an increasing role in treating neovascular AMD to help improve visual acuity (VA) outcomes, and prevent chronic decline in VA. This may lead to longer treatment free intervals and thus translate to a lesser treatment burden for many patients.

OPT-302 is a recombinant fusion protein that binds to and neutralises the activity of VEGF-C and VEGF-D by preventing ligand binding to the endogenous receptors, VEGFR-2, and VEGFR-3. It is highly specific for VEGF-C and VEGF-D and does not bind to VEGF-A.[2] Both VEGF-C and VEGF-D have been shown to induce vessel growth in several *in vivo* models,[29,30,31,32] and levels of VEGF-C and/or VEGF-D are upregulated in response to inhibition of VEGF-A with bevacizumab, ranibizumab or aflibercept.[33,34,35,36,37]

Additionally, VEGF-C has been specifically shown to play a critical role in the formation of the retinal vasculature.[38] VEGF-C is upregulated by inflammatory mediators that are implicated in the pathogenesis of the disease,[39] and elevated in the circulation of neovascular AMD patients compared to healthy volunteers.[40] [redacted]

2.2 Study Product

[redacted] OPT-302 binds and neutralises the activity of VEGF-C and VEGF-D by preventing ligand binding to endogenous VEGFR-2 and VEGFR-3.

Full details of the product (in terms of structure, formulation and mechanism of action) may be found in the Investigators' Brochure (IB).[2]

2.3 Pharmacodynamics

The molecular targets of OPT-302, VEGF-C and VEGF-D, are members of the VEGF family of secreted glycoproteins that are critical mediators of blood vessel growth (angiogenesis), lymphatic vessel growth (lymphangiogenesis) and vascular permeability. The vascular endothelial growth factors (VEGFs) bind to VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1) and/or VEGFR-3 (Flt-4), a family of structurally-related receptor tyrosine kinases that are predominantly expressed on the endothelial cells of blood and/or lymphatic vessels.[44,45] OPT-302 binds and neutralises the activity of both VEGF-C and VEGF-D, with high specificity, by preventing ligand binding to endogenous VEGFR-2 and VEGFR-3.

VEGF-C and VEGF-D induce angiogenesis *via* the activation of both VEGFR-2 and VEGFR-3, and

lymphangiogenesis *via* activation of VEGFR-3. VEGF-C and VEGF-D stimulate proliferation of endothelial cells *in vitro* and induce vessel growth in several *in vivo* models.[29,30,31,32,46,47] Furthermore, studies demonstrate that VEGF-C induces vascular permeability, mediated through the binding and activation of VEGFR-2.[48,49]

In vitro and *in vivo* studies implicate VEGF-C in the pathophysiology of neovascular AMD, notably the development of retinal vascularisation,[38] but also angiogenesis, lymphangiogenesis and vascular permeability in other tissues.[48,49]

[redacted]

Full details of the studies and mechanisms of activity may be found in the IB.[2]

2.4 Non-Clinical Safety

[redacted]

2.5 Clinical Studies

Clinical experience of intravitreal OPT-302 to date comprises three completed clinical studies: two studies of OPT-302 in combination with ranibizumab in participants with neovascular AMD (OPT-302-1001 and OPT-302-1002); and one study of OPT-302 in combination with aflibercept in participants with diabetic macular o/edema (DME) (OPT-302-1003). The study design and treatment groups for

each study are outlined in Table 2-1 below.

Table 2-1 Clinical Studies to Date

Protocol No.	Study Design	Treatment Groups	Study Population	N
OPT-302-1001	Phase 1 open-label, dose escalation study	• Ranibizumab + OPT-302 0.3, 1.0 or 2.0 mg, q4w x 3 • 2.0 mg OPT-302 monotherapy, q4w x 3	nAMD	51
OPT-302-1002	Phase 2b dose ranging, multicentre, double-masked, sham controlled study	• Ranibizumab + OPT-302 0.5 or 2.0 mg, q4w x 6 • Ranibizumab + sham, q4w x 6	nAMD	366
OPT-302-1003	Phase 1b/2a dose escalation study	• Aflibercept + OPT-302 0.3, 1.0 or 2.0 mg, q4w x 3 • Aflibercept + sham, q4w x 3	DME	153

Ranibizumab = 0 5 mg ranibizumab; q4w = administered every 4 weeks; nAMD = neovascular age-related macular degeneration; DME = diabetic macular oedema/edema; aflibercept = 2.0 mg aflibercept; N = number of participants

In the completed first-in-human clinical study (OPT-302-1001, n=51) in treatment-naïve or previously treated participants with neovascular AMD,[50] OPT-302 was well tolerated when administered every 4 weeks (total 3 doses) by intravitreal injection up to the highest dose tested (2.0 mg) in combination with 0.5 mg ranibizumab and as a monotherapy (2.0 mg OPT-302). No dose-limiting toxicities (DLTs) were observed, and the maximum tolerated dose (MTD) was not reached. In addition, preliminary signals of efficacy were observed.

[redacted]

[redacted]

Based on the positive Phase 2b study results in neovascular AMD, Opthea is conducting a prospective Phase 3 programme in treatment-naïve participants with neovascular AMD, of 2.0 mg OPT-302 in combination with 0.5 mg ranibizumab (OPT-302-1004) and of 2.0 mg OPT-302 in combination with 2.0 mg aflibercept (OPT-302-1005), compared with 0.5 mg ranibizumab or 2.0 mg aflibercept, with sham control in each trial respectively.

Full details of the outcomes for the completed clinical studies are provided in the IB.[2]

2.6 Rationale

The compensatory upregulation of VEGF-C and VEGF-D, and incomplete inhibition of the pathways mediating vascular growth, may be implicated in the sub-optimal responses seen with VEGF-A monotherapy. Therefore, combining OPT-302 with a VEGF-A inhibitor is expected to result in a more complete and effective inhibition of angiogenesis and vascular leakage in eyes with neovascular AMD compared to VEGF-A inhibition alone.

There is a high unmet medical need for more effective treatments in participants with sub-optimal responses to current treatments for neovascular AMD. [redacted]

[redacted]

3. STUDY OBJECTIVES

The criteria for evaluation of the study objectives are laid out in Section 10.1.

3.1 Primary Objective

To determine the efficacy of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 0.5 mg ranibizumab, in participants with neovascular AMD.

3.2 Secondary Objectives

The secondary objectives of the study are to determine the effects of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 0.5 mg ranibizumab from Baseline to (and at) Week 52 as determined by:

Efficacy:

- Changes in ETDRS BCVA letter score
- Changes in anatomical parameters (CNV area, SRF and IR cysts)

Safety:

[redacted]

3.3 Exploratory Objectives

[redacted]

4. STUDY OVERVIEW

This study is a Phase 3, multicentre, randomised, parallel-group, sham-controlled, double-masked, study of approximately 102 weeks in duration. Eligible study participants will be randomised at Baseline to one of three treatment arms in a 1:1:1 ratio: intravitreal ranibizumab followed by Standard Dosing 2.0 mg OPT-302; intravitreal ranibizumab followed by Extended Dosing 2.0 mg OPT-302; or intravitreal ranibizumab followed by a sham injection. The study has two phases, the Efficacy Phase (Baseline to Week 52 [redacted] and the Safety Phase [redacted] Although efficacy and safety will be assessed during both study phases, the efficacy of OPT-302 is intended to be characterised during the Efficacy Phase (*via* the primary and secondary efficacy endpoints), and the safety of OPT-302 after long term (2 year) administration is intended to be characterised during the Safety Phase.

During the Efficacy Phase (Baseline to Week 52), study medication will be administered according to the randomised schedule, commencing at the Baseline visit to Week 48. The primary endpoint will be determined at Week 52 [redacted] Once all study assessments have been completed at Week 52, the participant will enter the Safety Phase of the study [redacted] Each participant will continue to receive the study medication and dosing regimen allocated at Baseline. A final follow-up visit will be conducted at Week 100 [redacted] approximately 4 weeks after the planned last administration of study medication at Week 96 [redacted]

[redacted]

[redacted]

5. SELECTION OF STUDY POPULATION

To assess any potential safety concerns regarding participant eligibility, the Investigator is to refer to Section 6.11 and the IB[2] for detailed information regarding warnings, precautions, contraindications, AEs and other significant data pertaining to OPT-302, and the product label for data pertaining to ranibizumab.

The target population for recruitment is male or female participants aged at least 50 years, with a current diagnosis of neovascular AMD, and who have not received any prior therapy for neovascular AMD in the Study Eye.

To be eligible to enrol, participants must meet all the inclusion criteria and none of the exclusion criteria listed below at the Baseline visit. [redacted]

5.1 Inclusion Criteria

5.1.1 Study Eye

1. Active subfoveal CNV lesion or juxtafoveal CNV lesion [redacted] with foveal involvement [redacted] that is secondary to AMD. [redacted]
2. An ETDRS BCVA score between 60 and 25 (inclusive) letters.

5.1.2 General

1. Willing and able to provide written informed consent.
2. Male or female participants at least 50 years of age.
3. Able to understand and willing to comply with study protocol procedures and restrictions.

[redacted]

5.2 Exclusion Criteria

5.2.1 Study Eye

1. Any previous treatment for neovascular AMD, [redacted]

[redacted]

3. Clinically significant ocular disorders (other than neovascular AMD), which may, in the Investigator's opinion, interfere with assessment of BCVA, assessment of safety, or fundus imaging.

[redacted]

[redacted]

5.2.3 General

[redacted]

13. Any current (or history of a) social, psychological, or medical condition that, in the Investigator's opinion, should preclude enrolment into the study. [redacted]

[redacted]

5.3 Re-screening

[redacted]

5.4 Number of Participants

It is anticipated that approximately 990 eligible participants will be recruited into the study, with approximately 330 per study arm.

5.5 Participant Identification

Participants will be allocated a unique Participant Identification Number (PIN) at screening, and this number will be used to identify the participant for the duration of the study.

6. STUDY MEDICATION

6.1 Study Arm Allocation, Randomisation and Masking

6.1.1 Study Arm Allocation and Randomisation

[redacted]

[redacted]

6.1.2 Study Masking

[redacted]

[redacted]

[redacted]

6.2 Study Medication Details

The study medication comprises intravitreal administration of two study products:

- administration of the co-administered anti-VEGF-A therapy, 0.5 mg ranibizumab [50 µl volume]; [redacted]
- administration of the investigational product, 2.0 mg OPT-302 [50 µl volume], or a sham injection.

6.2.1 Investigational Product - OPT-302

The investigational product is OPT-302, [redacted]

6.2.1.1 Investigational Product Excipients

OPT-302 is formulated with the following excipients:

[redacted]

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[redacted]

6.2.1.2 Dose per Administration and Corresponding Justification

OPT-302 is administered at a dose of 2.0 mg per injection.

[redacted]

6.2.1.3 Supply, Packaging, and Labelling

OPT-302 is manufactured and packaged by Opthea, under current Good Manufacturing Practice (cGMP) conditions.

[redacted]

Each vial, and outer box, is packaged and labelled according to GMP and all regulatory requirements in each country participating in the study. [redacted]

6.2.1.4 Preparation of OPT-302 for Administration

[redacted]

6.2.2 Co-Administered Study Product - Ranibizumab

Ranibizumab will be administered as an intravitreal injection, at a dose of 0.5 mg (50 µL volume). The ranibizumab will be provided in commercial packaging and labelled for clinical trial use, and is to be stored, prepared, and administered as per the package insert. [redacted]

6.2.3 Control Arm and Sham Injection

[redacted]

6.3 Dosing Regimens and Corresponding Justifications

Study treatments are to be administered by intravitreal injection at the intervals described below, [redacted]

6.3.1 Dosing Regimen Justifications

6.3.1.1 Ranibizumab

Ranibizumab is to be administered as a fixed dose of 0.5 mg every 4-weeks. [redacted] the 4-weekly dosing schedule is the approved posology in the US,[10] [redacted]

6.3.1.2 OPT-302

OPT-302 is to be administered as a fixed dose of 2.0 mg every 4-weeks (Standard Dosing arm), or a fixed dose of 2.0 mg every 8-weeks, after 3 x 4-weekly loading doses (Extended Dosing arm).

[redacted]

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[redacted]

6.3.2 Standard Dosing Arm

Study products are to be administered from Baseline to [redacted] (Week 96) according to the following regimen, [redacted]

- 0.5 mg ranibizumab is administered at 4-weekly intervals from Baseline up to and including Week 96
- 2.0 mg OPT-302 is administered at 4-weekly intervals from Baseline up to and including Week 96.

[redacted]

6.3.3 Extended Dosing Arm

Study products are to be administered from Baseline to [redacted] Week 96) according to the following regimen, [redacted]

- 0.5 mg ranibizumab is administered at 4-weekly intervals from Baseline up to and including Week 96
- 2.0 mg OPT-302 is administered at 4-weekly intervals for three treatments [redacted] and then at 8-weekly intervals up to and including Week 96 [redacted]

[redacted]

- A sham intravitreal injection only is administered at visits where OPT-302 is not administered [redacted]

[redacted]

6.3.4 Control Arm

Study products are to be administered from Baseline to [redacted] Week 96) according to the following regimen, [redacted]

- 0.5 mg ranibizumab is administered at 4-weekly intervals from Baseline up to and including Week 96
- A sham intravitreal injection is administered at 4-weekly intervals from Baseline up to and including Week 96.

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4.1 Injection Procedure

[redacted]

[redacted]

[redacted]

6.5 Delay, Pause or Discontinuation of Study Product Treatment(s)

A delay in study treatments is defined as administration of one or both study products one or more days after the scheduled study visit has been completed. A pause in study treatments is defined as a temporary cessation of one or both study products for one or more of the study visits, with an intention to resume study treatment at the next or a subsequent study visit. Discontinuation is defined as a permanent cessation of one or both study products with no intention to restart treatment at a later study visit.

[redacted]

6.6 Emergency Unmasking Procedures

Emergency unmasking may only occur if the PI considers that knowledge of study medication is essential to properly treat a severe AE or an SAE, and the Treating Investigator cannot adequately treat the (S)AE. [redacted]

[redacted]

Whenever possible, the PI should discuss each case with the Medical Monitor and notify the Sponsor prior to unmasking - when this is not possible both the Medical Monitor and Sponsor must be notified as soon as is practical, and within 24 hours of unmasking taking place. The site's Independent/Research Ethics Committee (IEC/REC) / Institutional Review Board (IRB) should also be notified according to local regulations.

6.7 Dispensing and Accountability

The Unmasked Technician is responsible for ensuring accurate records of receipt, distribution, reconciliation, and return of study product. Accurate records must be kept regarding when and how much of each study product was administered to each participant in the study and what product was returned, with associated study product kit numbers and expiry dates.

At completion of the study, all unused study product must be reconciled *via* detailed records itemising all movement of study product to, from and within study sites, and dispensing records. Once reconciliation of study product has been performed, unused product (either returned dispensed or un-dispensed study product) may be destroyed or returned to the Sponsor or designee as per the Pharmacy Manual and written instructions issued by the Sponsor at the end of the study.

6.8 Assessment of Adherence to Study Medication

[redacted]

6.9 Investigator Initiated Rescue Medication

[redacted]

[redacted]

6.10 Other Concomitant Medication/Treatments

Permitted and prohibited concomitant medications and ocular treatments are outlined in detail in Section 7.3.

[redacted]

6.11 Risk Assessment

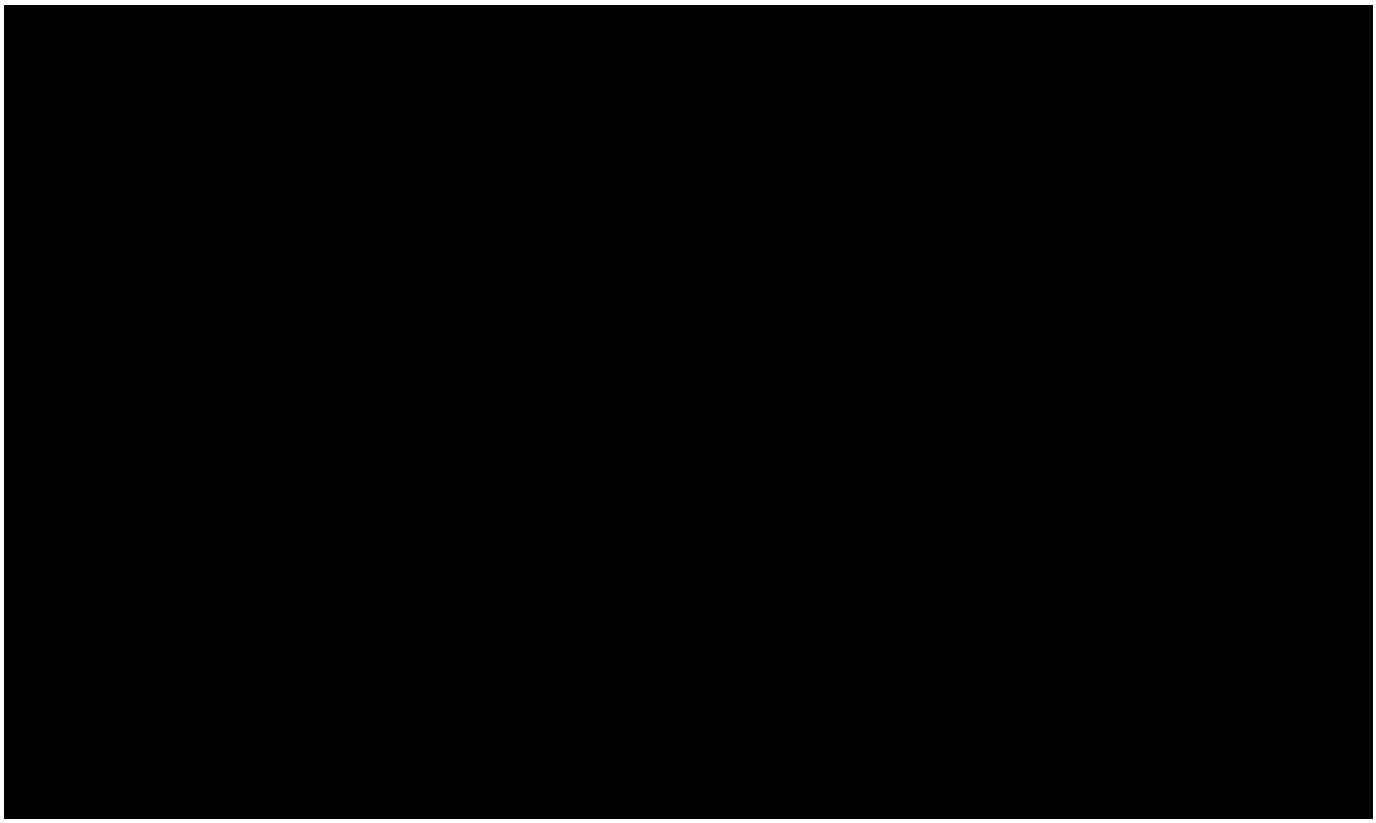
[redacted]

There appears to be no significant additional safety risks associated with the addition of OPT-302 to ranibizumab or aflibercept intravitreal therapy over and above those identified after intravitreal injection of anti-VEGF-A therapies, as observed to date [redacted]. The safety data is provided in more detail in the IB with a full benefit/risk evaluation.[2]

There are no anticipated additional risks to a participant relating to participation in this clinical trial due to the COVID-19 health emergency. Patients would require regular in-clinic treatment whether or not they were participating in a clinical trial, given the serious nature of neovascular AMD.

6.11.1 Ocular TEAEs

[redacted]



[redacted]

6.11.3 Precautions

OPT-302 should not be administered to participants with any of the conditions listed in the exclusion criteria [redacted]

As OPT-302 is still under development, there may be risks that are currently unknown which may be associated with the investigational product.

[redacted]

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[redacted]

Table 6-4 below presents the AEs that have been reported during clinical experience with intravitreal administration of well-established anti-VEGF-A therapies.[10,11,12,13]

Table 6-4 AEs Related to Intravitreal Anti-VEGF-A Therapies

Frequency	Rate*	Event(s)
Very Common	≥ 10% people	**Ocular:** Vitritis; vitreous detachment; retinal haemorrhage; visual disturbance; eye pain; vitreous floaters; conjunctival haemorrhage; eye irritation; foreign body sensation in eye; lacrimation increased; blepharitis; dry eye; ocular hyperaemia; eye pruritus; increased intraocular pressure. **Non-ocular:** sore throat; nasopharyngitis; headache and arthralgia.
Common	< 10% to ≥ 1% people	**Ocular:** Retinal degeneration; retinal disorder; retinal detachment; retinal tear; detachment of the retinal pigment epithelium; retinal pigment epithelium tear; visual acuity reduced; vitreous haemorrhage; vitreous disorder; uveitis; iritis; iridocyclitis; cataract; cataract cortical; cataract nuclear; cataract subcapsular; posterior capsule opacification; punctuate keratitis; corneal erosion; corneal abrasion; anterior chamber flare; vision blurred; injection site haemorrhage; eye haemorrhage; conjunctivitis; conjunctivitis allergic; eye discharge; photopsia; photophobia; ocular discomfort; eyelid oedema; eyelid pain; conjunctival hyperaemia. **Non-ocular:** urinary tract infection; anaemia; anxiety; cough; nausea; hypersensitivity; allergic reactions (rash, urticaria, pruritus, erythema).
Uncommon	< 1% to ≥ 0.1% people	**Ocular:** Hypopyon; hyphaema; keratopathy; iris adhesion; corneal deposits; corneal oedema; corneal striae; corneal epithelium defect; injection site pain; injection site irritation; abnormal sensation in eye; eyelid irritation; lenticular opacities.
Serious		
Common	< 10% to ≥ 1% people	Detachment or tear of the layer in the back of the eye, resulting in flashes of light with floaters progressing to a temporary loss of sight, or cataract.
Uncommon	< 1% to ≥ 0.1% people	Blindness, endophthalmitis with inflammation of the inside of the eye.

*CIOMS Definition; data sources: Lucentis® label and SmPC,[10,11] Eylea® label and SmPC.[12,13]

Full details of the non-clinical and clinical safety data for ranibizumab may be found in the package insert and the approved label for the product.

7. STUDY PROCEDURES AND EVALUATIONS

7.1 Assessment Periods and Study Procedures

7.1.1 Overview of Study Visits and Procedures

After screening assessments have been completed, eligibility has been confirmed, and Baseline assessments have been completed, participants will be randomised [redacted]

During the Efficacy Phase (Baseline to Week 52), study medication will be administered according to the randomised schedule, commencing at the Baseline visit, to Week 48. The primary endpoint will be determined at Week 52 [redacted] Once all study assessments have been completed at Week 52, the participant will continue the study in the Safety Phase (Week 52 to Week 100). Each participant will continue to receive study medication (per the schedule allocated at Baseline), resuming after all study assessments at Week 52, and continuing to Week 96 [redacted] except no loading doses are administered in the Extended Dosing OPT-302 arm. A final follow-up visit will be conducted at Week 100 [redacted], approximately 4 weeks after the last administration of study medication.

[redacted]

[redacted]

7.1.2 Visit Windows

[redacted]

7.1.3 Selection of the Study Eye

Only one eye may be "enrolled" into the study, and this eye will be designated the "Study Eye". This will be the eye that will be administered study medication and be assessed according to the protocol.

[redacted]

The Study Eye will be documented in the eCRF as either OD or OS.

7.1.4 Screening Evaluation

The screening evaluation period should be kept as short as possible so as to promptly commence medication for an eligible participant. [redacted]

[redacted]

[redacted]

7.1.5 Baseline Visit (Visit 2, Day 0)

The Baseline visit (Day 0) is to occur as soon as possible after eligibility has been confirmed, [redacted]

[redacted]

7.1.6 EFFICACY PHASE: [redacted]

[redacted]

[redacted]

7.1.7 Week 52 [redacted]

[redacted]

[redacted]

7.1.8 SAFETY PHASE: [redacted]

[redacted]

[redacted]

7.1.9 Final Study Visit: [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
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  [redacted]
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  - [redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.11 Interim Visits and Contact

Interim contact and visits between scheduled study visits may occur at any time during the study if requested by the participant, for the assessment of an AE, or as deemed necessary by the Investigator. [redacted]. All such unscheduled visits must be documented in the participant's study file and eCRF and any AEs reported during such visits will be documented in the eCRF.

7.1.12 Study Product Treatment Discontinuation

[redacted]

[redacted]

[redacted]

[redacted]

7.2 Observations and Measurements

7.2.1 Demographics, Medical and Surgical History

Each study participant's demographic information and medical and surgical history will be taken from medical records, clinic notes, and/or during the participant's interview at the screening evaluation.

7.2.1.1 Demographics

Study participants' gender, age (at the Screening Visit), race (and additionally ethnicity if in the US), [redacted] will be collected.

7.2.1.2 Medical and Surgical History

Relevant medical and surgical history will be collected, including: Any ongoing medical conditions or relevant conditions, any ocular surgical procedures, any ocular medical interventions, and all ophthalmic diagnoses.

7.2.1.3 Previous Ocular Treatments

All ocular treatments administered within the previous [redacted] should be recorded, with an indication of which eye (OS, OD, OU [*Oculus Uterque,* both eyes]) the treatment was administered to (if applicable).

Any previous treatment for neovascular AMD in the Study Eye is an exclusion for entry into the study, [redacted]

7.2.1.4 Prior Medication

All prescription and non-prescription medications, non-pharmaceutical therapeutic treatments, vitamin/mineral supplements and herbal or other complementary medicines taken or administered at Screening are to be recorded as prior medication, with start/stop dates or indicated as “ongoing”. [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.2.4 Ophthalmic Examination

Each participant is to undergo an ophthalmic examination at each study visit. All ophthalmic assessments are to be performed by a masked Assessing Investigator prior to study medication administration [redacted]

[redacted]

[redacted]

[redacted]

- [redacted] BCVA *via* the ETDRS System [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
    - [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

7.2.4.1 [redacted] Best-corrected Visual Acuity (BCVA)

[redacted]

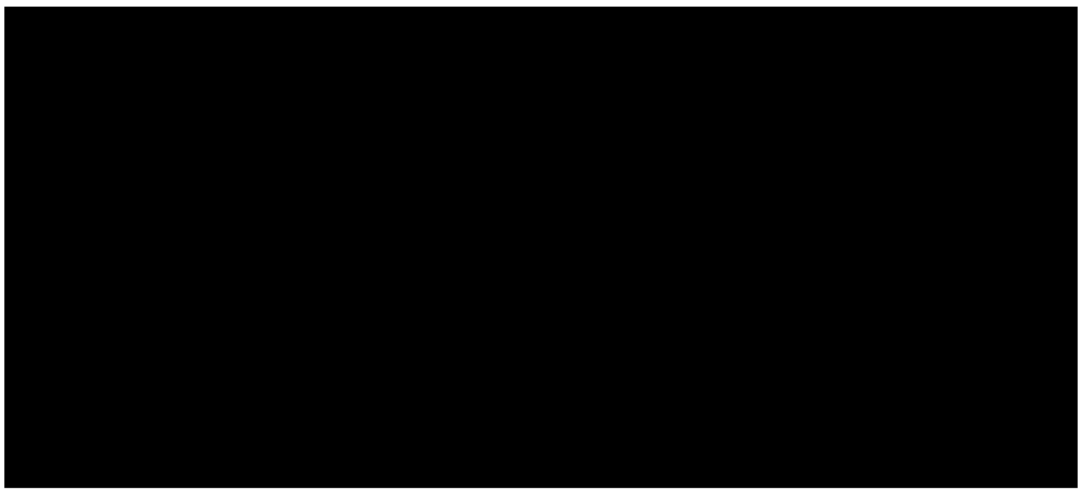
[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.6 *Adverse Events*

The Investigator(s) and designated study personnel will monitor each participant for AEs during the study. All AEs reported between the time consent was obtained and final follow-up is completed will be recorded in the eCRF. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3 Concomitant Medication and Treatments

7.3.1 Recording Concomitant Treatments

[redacted]

All medications must be reported and recorded in the eCRF (including prescribed and over-the-counter medications, vitamins, herbal remedies, other traditional preparations, and any ocular preparations administered of any type) [redacted]

[redacted]

7.3.2 Prohibited and Permitted Concomitant Treatment - Study Eye

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

7.3.3 Concomitant Treatment - Non-Study Eye

[redacted]

7.3.4 Other Prohibited Concomitant Treatments

[redacted]

8. SAFETY REPORTING

The reporting and documentation of AEs [redacted] is an essential component of all clinical studies. Therefore, it is important that all investigational staff understand the requirements and responsibilities outlined below. It is the responsibility of the Investigator to ensure that all AEs and other clinically significant findings that occur during the conduct of a clinical study are documented and reported accurately.

Adverse event(s) should be documented in terms of a medical diagnosis(es) where possible, rather than signs and/or symptoms.

8.1 Adverse Event Definitions

8.1.1 Adverse Event (AE)

[redacted]

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE (also referred to as an adverse experience) can be any unfavourable and unintended sign (*eg*. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

The Investigator will make a judgment regarding whether or not, in their opinion, the AE was related to the study product(s). However, even if the Investigator feels there is no relationship to the test product, the AE must be recorded. If any clinical AEs have occurred, they will be recorded on the AE report page of the eCRF and their severity will be graded.

Adverse events may include:

1. The significant worsening of a disease or symptoms of a disease.
2. An intercurrent illness.
3. Exacerbation (*ie.* increase in frequency or intensity) of a pre-existing condition or event.

An AE does not include a/an:

1. Medical or surgical procedure: but the *condition* that leads to the procedure is usually an AE.
2. Situation where an untoward medical occurrence has not occurred (*eg*. hospitalisation for cosmetic surgery, social and/or convenience admissions).
3. Overdose of either study drug or concomitant medication that does not result in any signs or symptoms. If any signs or symptoms of an overdose are present, then these will be recorded as an AE.

8.1.2 Treatment Emergent Adverse Event (TEAE)

A TEAE is an AE that was not present prior to treatment with the study product(s), or an event that was present prior to treatment, but worsens either in intensity or frequency following treatment.

8.1.3 Serious Adverse Event (SAE)

An SAE is defined as any AE that results in any of the following outcomes:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability / incapacity (including temporary or permanent

sight-loss)

- Is a congenital anomaly / birth defect
- Is an Important Medical Event, which includes an event that puts the participant at immediate risk of permanent sight loss.

[redacted]

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at immediate risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more serious.

Hospitalisation is defined as the participant being hospitalised > 24 hours, or the participant's hospital stay being prolonged for at least an additional overnight stay. Hospital admissions for a pre-existing condition, planned procedures, or for normal disease management procedures (*eg.* routine glycaemic control in a diabetic participant) will not be considered an SAE. Complications that occur during hospitalisations are usually AEs. If a complication prolongs hospitalisation by at least one night, it is an SAE.

Important Medical Events that may not result in death, be life-threatening, or require hospitalisation may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardise the study participant, may pose a serious risk to the participants vision, or may require urgent medical or surgical intervention to prevent one of the outcomes listed in the SAE definition. [redacted]

8.1.4 Adverse Drug Reaction (ADR) and Unexpected ADR

An Adverse Drug Reaction (ADR) is defined by the International Council for Harmonisation (ICH) as any noxious and unintended response to a medicinal product related to any dose. Therefore, it is any AE where there is reasonable possibility of a causal relationship between the study medication(s) and the AE.

An Unexpected ADR (UADR) is defined as an ADR, the nature, severity, or frequency of which, is not consistent with the applicable product information (*ie*. not listed in the IB for OPT-302 or in the Summary of Product Characteristics for ranibizumab [see Section 6.11]).

8.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as an SAE that is suspected to be an ADR, but is not consistent with the information provided in the Investigators' Brochure - *ie.* either is not listed as an expected ADR in the Reference Safety Information section of the IB, occurred at a greater severity than was listed, or there is an increase in the rate of occurrence that is judged to be clinically important.

All SUSARs must be reported to the applicable regulatory agencies within the timelines as stipulated by local law and guidelines by the Sponsor, and reported to each IEC/REC/IRB by each Investigator (see Section 8.9).

8.2 Timeframes for Reporting of an Adverse Event

8.2.1 Timeframe for Reporting Adverse Events

[redacted]

8.2.2 Timeframe and Timelines for Reporting Serious Adverse Events

[redacted]

[redacted]

8.3 Recording an Adverse Event

[redacted]

8.3.1 Assessment of Adverse Event Severity

Adverse event severity will be graded as per the current version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0).

AEs not presented in the CTCAE will be graded as follows:

Grade 1: Mild	An AE where there is an awareness of the sign or symptom, but no or minimal interference with normal daily activities.
Grade 2: Moderate	An AE that causes interference with normal daily activities

Grade 3: Severe An AE that causes inability to perform normal daily activities.

It should be noted that an AE that is considered to be "severe" may not necessarily be considered to be "serious" or of major medical significance.

8.3.2 Assessment of Adverse Event Causality

[redacted]

[redacted]

8.4 Study Product Administration Adverse Events

[redacted]

8.5 Ophthalmic Abnormalities as Adverse Events

[redacted]

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[redacted]

8.8 Follow-up of Adverse Events

Investigators must monitor participants with an SAE until the event has stabilised or resolved. In the case of non-serious AEs, follow-up should occur until the participant completes the study.

8.9 Regulatory Reporting Requirements

Opthea has a legal responsibility to notify the local regulatory authority(ies), and other overseas agencies (if applicable) about the safety of the product/drug under clinical investigation. Prompt notification of SAEs by the Investigator is essential so that legal obligations and ethical responsibilities towards the safety of other participants are met.

All SUSARs qualify for expedited reporting as soon as possible after Sponsor confirmation that the case meets the criteria for expedited reporting, and no later than the timelines stipulated by each relevant regulatory authority. Fatal or life-threatening SUSARs must be reported very rapidly by Sponsor (or designee) to the Regulatory authorities, with a maximum reporting timeline typically of 7 calendar days.

Therefore, it is essential that all SAEs are reported as soon as the site becomes aware that the event has taken place, in order for rapid triaging and notification to occur.

8.10 IEC/REC/IRB Reporting Requirements

The timeframe within which the Investigators must provide notification of deaths, study product related and/or unexpected SAEs is stipulated by the local regulatory authorities.

It is the Investigators' responsibility to comply with the requirements for the relevant IEC/REC/IRB notification. Each investigator will notify the relevant IEC/REC/IRB of all reportable events, [redacted]

[redacted]

[redacted]

9. CLINICAL MANAGEMENT

9.1 Participant Completion

In the context of clinical management, a participant will be deemed to have completed the study once all trial procedures have been completed to Week 100 (Visit 27). Any AEs or SAEs still ongoing will be followed in accordance with Section 8.

9.2 Minimising Study Participant Discontinuation

The Investigator should make every effort to keep each participant in the study [redacted] However, Investigator's efforts to retain participants must respect their ethical right to withdraw their consent and discontinue the study any time.

See Section 7.1.12 and Section 7.1.13 for procedures and evaluation of Study Product Treatment Discontinuation and Study Participation Discontinuation.

9.3 Lost to Follow-Up

Sites should make every effort to select participants who are motivated and give every indication that they will remain in the study to completion. If a participant fails to appear for a scheduled visit, the site must make all reasonable attempts to contact the participant, and work through any difficulties that the participant may be experiencing in attending the study visit. These attempts should be documented in the participant's study file.

9.4 Premature Termination of Study

The study may be terminated prematurely locally by the Sponsor, ethics, or regulatory authorities, if:

- The number and/or severity of AEs justify discontinuation of the study
- New data become available that raises concern about the safety of the investigational product so that continuation might cause unacceptable risks to participants.

In addition, Opthea reserves the right to discontinue the trial prior to inclusion of the intended number of participants, but will only exercise this right for reasons of safety or force majeure events.

After such a decision to discontinue the trial is made, the Investigator must contact all participants within two weeks, and written notification must be sent to the IRB/IEC.

9.5 End of the Study

The study is deemed to have ended once the last study visit has been completed for the last remaining participant.

10. STATISTICAL CONSIDERATIONS

[redacted]

[redacted]

11. HUMAN PARTICIPANTS PROTECTION

11.1 Regulatory Considerations

Opthea or their agents will submit the appropriate documents to the local regulatory agencies and IEC/REC/IRBs affiliated to each site and will await approval prior to study commencement.

This study will be conducted in accordance with the following guidelines and regulations as applicable:

- ICH Guidelines for Good Clinical Practice (GCP)
- The Declaration of Helsinki
- US Food and Drug Administration (FDA) Human Participant Protection Regulations (Title 21 Code of Federal Regulations, Parts 50, 54, 56 & 312).

11.2 Independent/Research Ethics Committee (IEC/REC)/Institutional Review Board (IRB)

Prior to the commencement of the clinical study, written approval from the IEC/REC or IRB must be received by the Investigator.

The Investigator or designee must submit the protocol, plus participant information and consent forms, for independent review by a recognised IEC/REC/IRB pertinent to the study location.

The IEC/REC/IRB should be constituted in accordance with local regulatory requirements.

[redacted]

11.4 Informed Consent

Written informed consent must be obtained from each potential study participants prior to the initiation of any study-related procedures. The Investigator or designee must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail, and the alternative treatment options including standard of care. The participant should be provided with sufficient time to consider the information, and be given the opportunity to ask questions. It is essential that the Investigator or designee fully explores the duration of the study with a potential participant and stresses the importance of attending all study visits, [redacted]

Each participant must be informed that participation in the study is voluntary, that he/she may discontinue participation in the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The information sheet accompanying the informed consent is to be given by means of a standard written statement, written in non-technical language, and potential participants should be given sufficient time to adequately read the information and properly consider the potential risks, benefits, study specific procedures and time commitments. The participant is to read and consider the consent statement before personally signing and dating it, and should be given a copy of the signed document. The participant must date the document, it is inappropriate for the PI or site staff to date the executed consent form. If participants' vision is too poor, participant consents, and provided that this is documented on the consent form, an impartial witness may be used to document consent. In this instance, any impartial witness is to be present for the full discussion, the documents are to be read and explained to the participant, and the participant (if able) and impartial witness should sign and date the ICF. In obtaining and documenting informed consent, the Investigator and his/her designee(s) will comply with applicable local and domestic regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the trial, site Investigators will have the IRB/IEC's written approval of the protocol, the ICFs, and any other study-related information to be provided to participants. The Sponsor (or designee) must review and confirm in writing that all essential documents have been received, prior to commencement of participant screening.

Participants will document their provision of informed consent by signing their informed consent forms.

The informed consent process will give individuals all of the relevant information and time they need in order to decide whether to participate, or to continue participation, in this study. All study related materials distributed to participants including the informed consent forms will be available in the local language(s). Potential participants will be permitted to ask questions and to exchange information freely with the study Investigators. Only listed study Investigators may obtain informed consent from potential study participants. The Investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

11.5 Ethical Considerations

The study involves intravitreal injections into the Study Eye which may cause anxiety and/or discomfort. In addition, since the study population comprises older participants, there may be some people with impairment of hearing, comprehension, or other disability. The Investigator and study staff must fully assess each potential participant to ensure that he/she is fully aware and fully understands the procedures and risks of the study. Potential participants who do not have the mental capacity to fully understand the nature of the study and potential risks must not be enrolled into the study.

11.6 Confidentiality

Members of the study site staff must all maintain participant confidentiality. The log of study participant names and other protected health information will be kept secured. [redacted]

Participant medical records pertaining to this study may be inspected/audited at any time by Opthea employees or their duly authorised representatives, a regulatory authority, or the IEC/REC/IRB. All records accessed will be strictly confidential. Consent to participate in this study includes consent to these inspections/audits.

The study will be conducted in accordance with data privacy regulations relevant to each participating country.

[redacted]

[redacted]

12. ADMINISTRATIVE ASPECTS

12.1 Clinical Trial Agreement

Prior to commencement of the study, the Principal Investigator must sign a clinical trial agreement that will clearly delineate the responsibilities and obligations of the Investigator and Sponsors and will form the contractual basis under which the clinical trial will be conducted.

12.2 Study File

All associated study correspondence will be filed by the Investigator and will be available for inspection by the study monitor and/or appropriate representatives of Opthea and/or regulatory authorities to determine that all documentation is present. It will be the responsibility of the Investigator to provide adequate means for organisation and filing of study documentation at the study centres.

12.3 Initiation of the Study

Prior to the commencement of the study, a designated representative of Opthea will visit the investigational site to ensure adequacy of facilities and to discuss with the Investigator, and other personnel involved with the study, their responsibilities with regard to protocol adherence. This visit may be waived in the event that there has been recent experience with the investigational site, and there has been no change to site facilities or key site staff.

The investigational staff may not enrol any participants prior to Opthea receiving written approval from the IEC/REC/IRB, and completion of a formal Site Initiation Meeting (SIV) conducted by an Opthea representative with key investigational site staff in attendance. This meeting will include an inventory of study supplies and a detailed review of the protocol and eCRFs.

12.4 Participant Reimbursement

Participants will be reimbursed according to the guidelines of the relevant IEC/REC/IRB in order to compensate them for items such as travel, meals, the inconvenience, and their time as appropriate.

12.5 Participant Identification and PIN

All participants who provide consent for the Study will be assigned a unique PIN. The PIN of the participant will be entered on all pages of the eCRF and any study specific documents and will be the participant's primary identification number.

12.6 Recording of Data

The Investigator should maintain the individual participant files [redacted] This constitutes 'source

data'. All entries on the eCRFs must be backed up by source data, unless agreed that the eCRF will constitute source data.

[redacted]

12.7 Monitoring of the Study

Monitoring for this study will be conducted both during monitoring visits and *via* centralised review of eCRF data.

The Investigator will permit Opthea and their agents to monitor the study as frequently as Opthea deems necessary to determine that data recording and protocol adherence are satisfactory. A designated representative of Opthea in the form of a study monitor will verify participant data on the eCRFs for the purpose of analysis.

The Investigator will allow Opthea and their agents reasonable access to the related source documents for monitoring purposes as frequently as the sponsor deems necessary. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

12.8 Protocol Deviations

Deviations from the protocol should not be made other than as part of a protocol amendment agreed upon with Opthea, except where necessary to eliminate an immediate hazard to study participants or when the change(s) involves only logistical or administrative aspects of the study.

All protocol deviations must be noted and explained in the Investigator's file.

[redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]

[redacted]

12.9 Quality Management

Prior to study start, all risks to critical study processes and data will be identified, both at the system level, and clinical trial level. A risk review and control process will be implemented, and risks will be monitored throughout the study to ensure that appropriate actions and processes are instigated.

Throughout the Study, the data will be monitored (both locally and remotely) and the eCRFs checked against the participant's medical record for completeness and accuracy. This will be performed by Opthea or its legally contracted agents.

Following completion of the eCRFs, the data will be electronically checked for consistency and range. Queries will be generated for spurious data and clarification sought from the responsible Investigator or delegate at the Study site. These data queries must be resolved in a timely manner by the Study site.

12.10 Quality Assurance Audit/Inspection

The Study may be subject to an audit by an authorised representative of Opthea and/or an authorised Regulatory Authority (*eg.* FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]).

Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. Opthea will immediately notify the Investigator of an upcoming audit/inspection. The PI must also notify Opthea if they are made aware of an audit that may involve this study, or the facilities.

In the event of an audit, all pertinent study-related documentation must be made available. If an audit or inspection occurs, the Investigator will permit the auditor/inspector direct access to all relevant documents and allocate his/her time as well as the time of relevant staff to discuss the findings and any relevant issues.

12.11 Study and Site Closure

Opthea reserves the right to prematurely discontinue or suspend the study either at a particular site for significant quality or compliance issues, or at a particular site or all sites at any time for safety reasons or due to a force majeure event. If such action is taken, Opthea will discuss this with the Investigator(s) at that time and notify the Investigator(s) in writing. If the study is suspended or terminated for safety reasons all Investigators conducting the study will be immediately notified of the action as well as the reason for it, as will the relevant regulatory agencies. The Investigator is responsible for advising the IEC/REC/IRB overseeing the study at their site of any study and/or site closure.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted].

12.12 Record Retention

All study documents, including the protocol and IB, are the confidential property of Opthea and should be regarded as such. [redacted]

Following completion of the study the Investigator will retain copies of the approved protocol, approved protocol amendments, completed eCRFs, informed consent documents, relevant source documents, and all other supporting documentation related to the project in accordance with the applicable IEC/REC/IRB, ICH and regulatory requirements (whichever is the longer). [redacted]

[redacted]

12.13 Study Report

A complete study report and its results shall be written on completion of the study and will include any conclusions drawn with respect to the safety and efficacy of the study product (refer to ICH Topic E3 - Note for Guidance on Structure and Content of Clinical Study Reports [CPMP/ICH/137/95]).

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13. SPONSOR RESPONSIBILITIES

In addition to preparing the study protocol Opthea or their agents will also be responsible for the conduct of the activities listed below.

13.1 Funding

Opthea will fund the study as outlined in the clinical trial agreements. All direct costs associated with the conduct of the study and laboratory investigations will be paid for by Opthea as outlined in the clinical trial agreements.

13.2 Supply of Study Materials and Study Documentation

Opthea or their agents will supply all the study materials and templates and other associated documentation required for the study.

13.3 Compliance with Regulatory Requirements

Opthea will ensure that the Investigator is conducting the study in accordance with the local and international regulatory requirements as stipulated in the protocol.

13.4 Transfer of Sponsor Obligations

Transfer of Sponsor obligations may occur for certain activities such as project management, monitoring and data management. Such transfer of obligations will be outlined in a specific agreement, and will not discharge the Sponsor of the obligation to ensure proper oversight of all aspects of the study.

14. USE OF DATA AND PUBLICATIONS

Opthea may disclose data derived from the study to other Investigators and regulatory authorities in one or more geographical regions.

The principles for publication of results of this study will be addressed in clinical trial agreements between Opthea and the study site, and Opthea and the subcontractors performing the study. Results means any and all information and know-how (whether patentable or not) which is discovered, invented or developed or which arises in the course of or as a result of the conduct of the Study, including any and all improvements to the products being studied.

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