# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| Title: | A Global, Phase III, Double Blind, Randomized Controlled Study to Compare the Efficacy, Safety & Immunogenicity of LUBT010 with Lucentis® in Patients with Neovascular Age-Related Macular Degeneration. |
| Protocol No. | LRP/LUBT010/2016/008<br>Version No.: 2.2, Dated 19 May 2022<br>Supersedes: Version No.: 2.1, Dated 20 Apr 2021 |
| EudraCT number | 2017-004409-42 |
| Name of Study Drug: | Ranibizumab (LUBT010) |
| Development Phase: | Phase III |
| Sponsor: | Lupin Limited (Biotechnology Division)<br>Gat No: 1156, Village-Ghotawade,<br>Taluka-Mulshi, Pune. Pin: 412115<br>Maharashtra, India |
| Sponsor Signatory: | [redacted] |



This study will be conducted according to the protocol and in compliance with the International Council for Harmonization- Good Clinical Practice (ICH GCP E6 R2) and applicable regulatory requirements.

## SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Global, Phase III, Double Blind, Randomized Controlled Study to Compare the Efficacy, Safety & Immunogenicity of LUBT010 with Lucentis® in Patients with Neovascular Age-Related Macular Degeneration.

PROTOCOL NUMBER: LRP/LUBT010/2016/008

[redacted]

[redacted]

# STUDY SYNOPSIS

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Lupin | **Protocol No.:** **LRP/LUBT010/2016/008** | |
| **Name of Active Ingredient:** Ranibizumab | | |

**Title of Study:**

A Global, Phase III, Double Blind, Randomized Controlled Study to Compare the Efficacy, Safety & Immunogenicity of LUBT010 with Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

**Study Sites:**

Approximately 75-100 sites across Europe, United States (US), and India having ophthalmologists who are experienced in diagnosing and treating neovascular age-related macular degeneration (AMD)

**Development Phase:** Phase III

**Objectives:**

**Primary Objective:**

To demonstrate the equivalence in efficacy of LUBT010 to Lucentis® in terms of visual acuity, in patients with Neovascular Age-Related Macular Degeneration.

**Secondary Objectives:**

- To assess the safety and tolerability of LUBT010 as compared to Lucentis®.
- To assess the immunogenicity of LUBT010 as compared to Lucentis®

**Study Design:**

Global, Phase III, Double Blind, Randomized Controlled, two-arm, interventional study in patients with neovascular AMD.

**Methodology:**

Eligible patients with Neovascular AMD will be randomly assigned to receive either LUBT010 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) once monthly (intravitreal injection) or Lucentis® 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) once monthly (intravitreal injection) for 12 months.

Patients will be randomized on Day 1. Only one eye per patient will receive the investigational product (IP).

Patients will visit site for a safety visit after the first dose on any day from Day 2 to Day 9, followed by the next visit on Day 31 ± 2 days, and thereafter monthly for a total of 12 months (i.e. Day 61, Day 91, Day 121, Day 151, Day 181, Day 211, Day 241, Day 271, Day 301, Day 331, and Day 360), with an allowable visit window period of ± 2 days. A post injection visit/ telephonic safety assessment after every injection will be done as deemed necessary by Investigator. Efficacy, safety, and immunogenicity assessments will be done periodically.

Day 360 ± 2 will be End of Study (EOS) visit.

**Number of Patients:**

Adequate number of patients will be screened to randomize approximately 600 patients to 2 treatment arms in 1:1 ratio to have approximately 558 evaluable patients.

**Diagnosis and Main Criteria for Inclusion:**

Ambulatory male and female patients aged ≥50 years with active choroidal neovascularization (CNV) lesions involving the foveal center secondary to neovascular AMD, who are anti-VEGF naïve and having best corrected visual acuity (BCVA) in the study eye between 20/40 and 20/200 (Snellen equivalent), using Early Treatment Diabetic Retinopathy Study (ETDRS) chart testing.

**Investigational Product:**

The IPs will be supplied as:

**Test Product**: LUBT010 supplied as single-use, 2-cc glass vial containing 2.3 mg of ranibizumab in 0.23 mL solution designed to deliver 0.05 mL of 10 mg/mL ranibizumab, by intravitreal injection.

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|---|---|---|
| **Name of Sponsor/Company:** Lupin | **Protocol No.:** **LRP/LUBT010/2016/008** | |
| **Name of Active Ingredient:** Ranibizumab | | |

**Reference Medicinal Product:** EU-approved Lucentis® supplied as single-use, 2-cc glass vial containing 2.3 mg of ranibizumab in 0.23 mL solution designed to deliver 0.05 mL of 10 mg/mL ranibizumab, by intravitreal injection.

**Dose and Administration:**

Ranibizumab 0.5 mg (Lucentis® or LUBT010) will be administered once every month as intravitreal injection for 12 months. Total 12 injections would be given to each patient.

**Study Duration:** Approximately 13 months

- Screening Period: Maximum 28 days
- Treatment and Subsequent Assessments: 12 months

**Study Endpoints:**

**Primary Endpoint:**

Mean change in BCVA from baseline in the study eye at the end of 12 months, assessed with the ETDRS chart.

**Secondary Endpoints:**

**Efficacy:**

- Mean change in BCVA from baseline in the study eye at the end of 3 months assessed with the ETDRS chart.
- Mean change in BCVA from baseline in the study eye at the end of 6 and 9 months, assessed with the ETDRS chart.

**Safety:**

- Adverse Events (AE) assessment, ocular and non-ocular
- Ophthalmic examination
- Physical and systemic examination
- Vital signs
- Electrocardiogram (ECG)
- Laboratory parameters: Blood (hematology and biochemistry) and urinalysis

**Immunogenicity:**

Proportion of patients with anti-drug antibodies at the end of 1, 3, 6, 9, and 12 months.

**Exploratory Endpoint:**

- Mean change from baseline in National Eye Institute Visual Functioning Questionnaire – 25 (NEI-VFQ-25) Version 2000 (interviewer administered) scores at 3, 6, and 12 months.

**Statistical Methods:**

The primary endpoint of change in BCVA from baseline in the study eye at the end of 12 months will be analyzed using ANCOVA model with treatment as fixed effect, and baseline BCVA as covariate. The equivalence of efficacy will be assessed based on 90%[#] (two-sided) confidence interval for the difference in mean change in BCVA from baseline in the study eye at end of 12 months, with an equivalence margin of 4 letters. ([#] As generally required by US Food and Drug Administration [FDA])

Similarly, the equivalence of efficacy will be assessed based on 95%[##] confidence interval of the difference in mean change in BCVA from baseline in the study eye at the end of 12 months, with an equivalence margin of 4 letters. ([##] As generally required by the European Medicines Agency [EMA].)

For continuous data, summary statistics will include the number, arithmetic mean, standard deviation (SD), median, minimum, and maximum. For categorical data, frequency and percentage will be presented.

The safety data and immunogenicity data will be summarized and listed.

## Table 1: Schedule of Assessment

| Mon=Months d=day Rand=Randomization | Screening Period | Treatment & Assessment Period (12 months) | | | | | | | | | | | | | EOS/ Early Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit | Rand | Safety Visit | 1 mon @ | 2 mon @ | 3 mon @ | 4 mon @ | 5 mon @ | 6 mon @ | 7 mon @ | 8 mon @ | 9 mon @ | 10 mon @ | 11 mon @ (EOT) | 12 mon[21] (EOS) |
| | (Max 28 days) | Day 1[#] | On any day from Day 2 to 9 | Day 31 ± 2 d | Day 61 ± 2 d | Day 91 ± 2 d | Day 121 ± 2 d | Day 151 ± 2 d | Day 181 ± 2 d | Day 211 ± 2 d | Day 241 ± 2 d | Day 271 ± 2 d | Day 301 ± 2 d | Day 331 ± 2 d | Day 360 ± 2 d |
| Informed consent | X | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | |
| Eligibility criteria assessment | X | X[1] | | | | | | | | | | | | | |
| Medical & Surgical history (including Ophthalmic history) | X | | | | | | | | | | | | | | |
| Physical & Systemic examination | X | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs[2] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X | | | | | | | | | | | | | | |
| Blood sampling for laboratory investigations[3] | X[4] | | | | | X | | | X | | | X | | | X |
| Urine sample for routine analysis[3] | X | | | | | X | | | X | | | X | | | X |
| Urine Pregnancy Test[5, 6] | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum Pregnancy test[5,6] | X | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ECG[7] | X | | | | | | | | X | | | | | | X |
| IP administration (study eye only)[8] | | X[8] | | X[8] | X[8] | X[8] | X[8] | X[8] | X[8] | X[8] | X[8] | X[8] | X[8] | X[8] | |
| Adverse event assessment[9] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication/ treatment[10] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Refraction assessment[11] | X[12] | X[13] | | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X |
| BCVA with ETDRS starting @ 4 meters[11] | X[12] | X[13] | | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X |
| Ophthalmoscopic examination (Indirect dilated) | X | X[14] | X | X[14] | X[14] | X[14] | X[14] | X[14] | X[14] | X[14] | X[14] | X[14] | X[14] | X[14] | X |
| Slit lamp examination | X | X[13] | X | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X[13] | X |
| Intraocular pressure measurement[15] | X | X[16] | X | X[16] | X[16] | X[16] | X[16] | X[16] | X[16] | X[16] | X[16] | X[16] | X[16] | X[16] | X |
| Fluorescein angiography[17,18] | X | | | | | | | | | | | | | | |
| Optical coherence tomography (OCT)[17] | X[19] | | | | | | | | | | | | | | |
| Blood sampling for Immunogenicity[13, 20] | | X | | X | | X | | | X | | | X | | | X |
| NEI-VFQ-25 | | X | | | | X | | | X | | | | | | X |

Explanation of symbols used:

@ A post injection visit/ telephonic safety assessment after every injection will be done as deemed necessary by Investigator.

# In the situation where the day of first dosing is different from day of randomization, all the visit days should be calculated from Day 1 (day of first dosing) rather than day of randomization.

1 Confirmation of eligibility (based on screening results and Investigations done on Day 1)

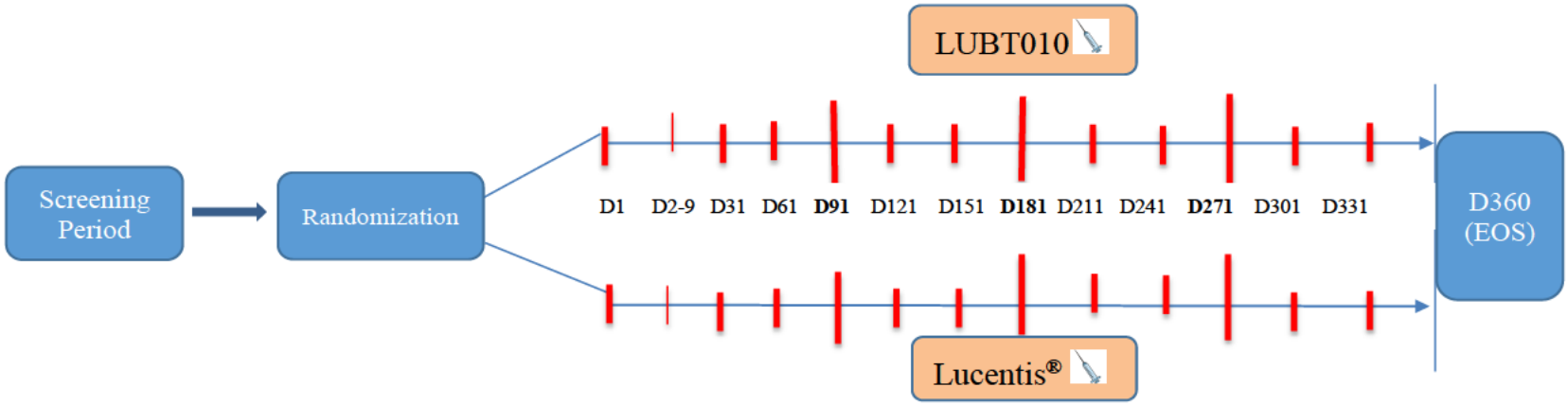
2 Includes body temperature, pulse rate, blood pressure, and respiratory rate. Should be done pre & post treatment on injection days.

3 **Hematology:** Complete blood count (CBC) [haemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), platelets, and differential blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils)]

**Blood chemistry:** Bilirubin (total, direct, indirect), alkaline phosphatase, ALT, AST, BUN, total protein, albumin, globulin, uric acid, urea, creatinine, random glucose **Urinalysis:** Appearance, color, specific gravity, pH, protein, glucose, ketones, urobilinogen, occult blood (and microscopic examination). (Repeat test can be conducted, if required. Additional investigations may be performed at the discretion of investigator to ensure subject safety.)

4 Including Serology: HIV, HBV (HbsAg), HCV, and Syphilis (RPR). Follicle stimulating hormone (FSH) to be done in all females at screening.
5 To be done in females of childbearing potential (females who are not surgically sterile or menopausal).
6 Serum/ Urine pregnancy test can be repeated anytime in local/ central laboratory when pregnancy is suspected in any female patient. Urine pregnancy test to be performed by the female patients themselves and the results reported to site during the visit.
7 Electrocardiogram (ECG) assessment can be done during any of the visits if the patient complains of any symptoms pointing towards a cardiovascular condition.
8 Drug to be administered as per recommendations (e.g. prophylactic antimicrobial therapy, aseptic precautions, monitoring for AEs). Patient will be observed for at least 60 min (± 30 min) post injection. Interval between 2 intravitreal injections of ranibizumab should not be less than 28 days
9 Elicit reports of any decrease in vision, eye pain, unusual redness or any other new ocular symptoms in the study eye, or any other AEs. On drug administration visits, AE assessment will be performed pre and postdose.
10 Includes medication for previous treatment for AMD or any other ocular condition within 3 months prior to screening and Protocol specified procedural medications (e.g. dilating drops, fluorescein dyes etc.) and pre & post medications used by the patients or any other systemic treatments
11 To be performed prior to dilating eyes by technicians trained and qualified to measure BCVA. BCVA assessment should begin at a starting distance of 4 meters.
12 Refraction and Visual acuity testing should be done prior to other ophthalmic investigations during screening. Only when the patient is eligible based on BCVA, the remaining investigations should be done. The order in which various other procedures are performed may vary from clinic to clinic, provided the procedures are completed within screening period.
13 To be performed pre-treatment
14 Predose (both eyes) & Post dose (study eye only)
15 Measurement method used for a patient to be preferably consistent throughout the study
16 Obtained pre-treatment for both eyes and 60 min (± 30 min) post injection for study eye only
17 Fundus photographs/ soft copy to be retained as source document
18 Known history of sensitivity to fluorescein dye to be checked before Fluorescein angiography
19 To be done in both eyes at screening and in study eye after every injection within a month unless not considered necessary by PI as decided by clinical examination.
20 Blood samples for immunogenicity to be collected, before dosing study drug (predose) at Day 1, Day 31, Day 91, Day 181, Day 271, and at EOS visit (Day 360).
21 In case of early discontinuations/ premature termination of the study all EOS investigations should be done on the day of termination as far as possible.

**Figure 1: Study Flow Chart**




- D = Day
- 💉 - Lucentis® or LUBT010 injection to be given intravitreally for 12 months at following monthly visits: D1, D31, D61, D91, D121, D151, D181, D211, D241, D271, D301, and D331 with an allowable visit window period of ± 2 days.
- Patients will visit site for a safety visit after the first dose on any day during Day 2 to 9. A post injection visit/ telephonic safety assessment after every injection will be done as deemed necessary by Investigator. Day 331 will be the End of Treatment (EOT) visit and Day 360 will be the End of Study (EOS)visit.
- Efficacy & Safety assessments will be done at monthly visits. Immunogenicity testing will be done at Day 1 and at the end of 1 month (D31), 3 months (D91), 6 months (D181), 9 months (D271), and 12 months (D360).

# 1 TABLE OF CONTENTS

## 1.1 List of Tables



## 1.2 List of Figures

## 2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Full form |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Events |
| ALT | Alanine Transaminase |
| AMD | Age-Related Macular Degeneration |
| APROP | aggressive posterior retinopathy of prematurity |
| AST | Aspartate Aminotransferase |
| BCVA | Best Corrected Visual Acuity |
| BUN | Blood Urea Nitrogen |
| CNV | Choroidal Neovascularization |
| CRF/ eCRF | Case Report Form/ electronic Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DME | Diabetic Macular Edema |
| DR | Diabetic Retinopathy |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| EMA | European Medicines Agency |
| EOS | End of Study |
| EOT | End of Treatment |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| EU | European Union |
| FA | Fluorescein Angiography/ Fundus Fluorescein Angiography |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HBV | Hepatitis B virus |
| HbsAg | Hepatitis B surface Antigen |
| HCV | Hepatitis C virus |
| HIV | Human Immunodeficiency Virus |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IOP | Intraocular pressure |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| mCNV | Myopic Choroidal Neovascularization |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minutes |
| NEI-VFQ-25 | National Eye Institute Visual Functioning Questionnaire - 25 |
| ºC | Degree Celsius |
| OCT | Optical Coherence Tomography |
| ºF | Degree Fahrenheit |
| IGS | Immunogenicity Analysis Set |
| PCT | Pre-clinical Toxicity |
| PPS | Per Protocol Analysis Set |

| Abbreviation | Full form |
|---|---|
| RMP | Reference Medicinal Product |
| ROP | retinopathy of prematurity |
| RPR | Rapid Plasma Reagin |
| RVO | Retinal Vein Occlusion |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SMP | Safety Monitoring Plan |
| SUSAR | Suspected Unexpected Serious Adverse Drug Reaction |
| TEAE | Treatment Emergent Adverse Events |
| US | Unites States |
| VEGF | Vascular Endothelial Growth Factor |
| VEGF-A | Vascular Endothelial Growth Factor A |
| WHO | World Health Organization |

**Definition of Terms**

| Term | Definition |
|---|---|
| AMD | Clinical and/or angiographic signs consistent with AMD (e.g., drusen, retinal pigment epithelial changes, choroidal neovascularization (CNV) with no other likely etiologic explanations for the degenerative changes |
| CNV lesion | A contiguous area of abnormal tissue in the macula that encompasses angiographically documented CNV with possible additional components of subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and fibrosis |
| Active CNV lesion | Active CNV includes any leakage on fluorescein angiography (FA)or Optical Coherence Tomography (OCT) |
| Primary CNV lesion | Newly diagnosed and previously untreated |
| Recurrent CNV lesion | Previously diagnosed and regressed but currently presenting with a new, active component |
| Sub-foveal | Including the center of the fovea within the boundaries of the CNV |
| Best Corrected Visual Acuity BCVA | The best possible vision that an eye can achieve with the use of glasses or contact lenses i.e. after correcting the refraction error. |
| Effective Contraception/ birth control | Effective methods of birth control in this study include hormonal birth control (eg, combined estrogen and progestogen containing [oral, intravaginal, or transdermal] or progesterone only [oral, injectable, or implantable] hormonal contraception associated with inhibition of ovulation, intrauterine devices, intrauterine hormone releasing system, bilateral tubal ligation, vasectomized partner, or sexual abstinence). |
| End of Trial | Last patient last visit. |
| Menopause | History of physiological amenorrhea since past 1 year or FSH value indicating menopause with high reliability |

# 3 INTRODUCTION

## 3.1 Background

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness among people who are 50 years of age or older in the developed world. AMD has become an important and increasing cause of retinal blindness in developing countries, along with Diabetic Retinopathy (DR)in adults[1].Globally, AMD ranks third as a cause of blindness after cataract and glaucoma. The main risk factor is ageing. Other risk factors may include the use of tobacco, genetic tendencies, the degree of pigmentation (with light colored eyes being at higher risk), arterial hypertension, the ultraviolet rays, and consumption of a non-balanced diet.[2]There is some evidence that links both cardiovascular and inflammatory biomarkers to AMD. The genetic etiology of AMD continues to be an area of research and investigation.[3]

Age-related macular degeneration (AMD) is a chronic degenerative disorder of the retina that causes progressive loss of central vision and is a leading cause of blindness in older adults.[4] Age-related macular degeneration is classified into two different types: the non-exudative (or dry) form and the exudative (wet or neovascular) form. The dry form is the most prevalent, accounting for 90% of the cases. The onset and progression of either type do not follow any particular pattern. It is not uncommon that the dry form develops into the wet form of AMD in which new choroidal vessels are developed. The latter form causes the worst incapacity and accounts for approximately 90% of severely impaired vision in AMD. In this process, the oxygen supply to the macula is disrupted and as a response to ischemia, new, immature, leaky blood vessels are formed. These may grow through breaks of the membrane behind the retina, towards the macula, often lifting the retina and causing hemorrhage in the sub-retinal space. Eventually, the lesions may turn into scars resulting in destruction of the macula and loss of central vision. The angiographic classification of AMD lesions includes determination of the lesion size, the proportion of the entire AMD lesion that consists of ‘classic’, minimally classic, and ‘occult’ choroidal neovascularization (CNV).[5]

The World Health Organization (WHO) estimates that neovascular AMD affects 3 million people globally, accounting for 8.7% of all blindness and 50% of blindness in industrialized countries.[6] The global prevalence of AMD is expected to increase to 288 million by the year 2040.[7].If left untreated, the visual prognosis for eyes with neovascular AMD is poor. Also, AMD adversely affects quality of life and activities of daily living, causing many affected individuals to lose their independence in their retirement years.[3]
Although neovascular AMD (nAMD) accounts for only 10%–20% of the overall cases of AMD, it accounts for 80% to 90% of AMD-associated vision loss. For neovascular AMD, the visual loss is progressive. Patients with unilateral nAMD have a 4% to 12% risk of CNV developing in the second eye 1 year after diagnosis, and between 20% and 42% of such patients harbor the risk of CNV developing 2 to 3 years after diagnosis. Although, no complete cure exists, the available treatment options maintain or improve vision, or both.[8]

Vascular endothelial growth factor (VEGF) has been implicated as playing an important role in the pathogenesis of neovascular AMD. Vascular endothelial growth factor A (VEGF-A), a diffusible cytokine that promotes angiogenesis and vascular permeability, has been implicated as an important factor for promoting neovascularization.[9]

Introduction of VEGF anti-angiogenesis therapy produced a true paradigm shift in the treatment of neovascular (wet) AMD. Anti-angiogenic therapy, aimed at halting abnormal blood vessel growth, became recognized as an entirely new class of disease treatment and has become the first line of treatment in neovascular-AMD.[6] However, pegaptanib, the first anti-VEGF agent although reduced the rate of vision loss, did not show significant improvement in vision. Off-label use of bevacizumab for neovascular AMD raised safety concerns due to the potential increased incidence of arterial thromboembolic events. Besides bevacizumab being a full-length antibody was thought to be difficult to penetrate all the layers of retina & choroid. Therefore, ranibizumab was engineered as a recombinant humanized immunoglobulin G1 kappa isotype monoclonal antibody fragment with a small molecular size and lack of Fc portion of the antibody which eliminates the possibility of complement-mediated or cell-dependent cytotoxicity triggered by interaction of the Fc receptors with inflammatory cells. Since the introduction of ranibizumab, the monoclonal antibody fragment against all isoforms of VEGF-A, anti-VEGF therapy revolutionized the treatment of neovascular AMD and other VEGF related retinal diseases. Ranibizumab not only halted the vision loss but also increased the visual acuity with lesser of systemic VEGF related adverse events (AEs).

Lupin has developed an investigational biosimilar of ranibizumab (referred as LUBT010 in this clinical study protocol) and intends to conduct a clinical study in order to market the product in global markets (United States [US], European Union [EU], and India). As per regulatory requirements, quality parameters have been established and a Pre-clinical Toxicity (PCT) study has shown that LUBT010 is safe in doses tested (up to 3 times human dose) and well tolerated when given as intravitreal injection. The planned Phase III study will provide data on similarity of Lucentis® and LUBT010 in terms of efficacy, safety and immunogenicity.

### 3.2 Scientific Findings [10,11]

Innovator's ranibizumab (Lucentis®)/ the Reference Medicinal Product (RMP) was approved in 2006.
Lucentis® is indicated in adults for the treatment of Neovascular (wet) Age-related Macular Degeneration (AMD), Macular edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) and Myopic Choroidal Neovascularization (mCNV). Lucentis® is also indicated in preterm infants for: Treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or APROP (aggressive posterior ROP) disease.
Ranibizumab is administered 0.5 mg (0.05 mL) by intravitreal injection once a month (approximately 28 days).

Based on the population pharmacokinetic analysis of patients with neovascular AMD, maximum serum concentrations reached at approximately 0.5[12] to 1 day after monthly intravitreal administration of ranibizumab 0.5 mg/eye. The apparent half-life of ranibizumab in serum after intravitreal administration was equivalent to the vitreous elimination half-life (approximately 9 days). Steady-state minimum concentration was 0.22 ng/mL with a monthly dosing regimen. Systemic exposure range was 1.7 (±1.1) ng/mL, which was below the concentration necessary to inhibit the biological activity of VEGF-A by 50% (11 to 27 ng/mL). Due to the negligible and variable systemic exposure after intravitreal administration, systemic pharmacokinetics (PK) is not considered surrogate of efficacy which is measured in terms of

visual acuity. In humans, although the serum ranibizumab concentrations were several-fold lower than vitreal concentrations, some systemic side effects related to anti-VEGF have been observed. However, data available from the 2-year MARINA study has demonstrated that those events that were considered of specific concern (ie, arterial thromboembolic events) were more balanced between sham and active arms.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly or renal impairment status). The systemic exposures are very low after ocular administration, but due to its mechanism of action, ranibizumab is regarded as potentially teratogenic and embryo-/fetotoxic and must not be used in pregnant and lactating women unless absolutely needed due to the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment. Safety has not been established in nursing women or pediatric patients; breast-feeding is not recommended during the use of ranibizumab.

The most frequently reported ocular adverse reactions following injection of Lucentis® are eye pain, ocular hyperemia, increased intraocular pressure, vitritis, vitreous detachment, retinal hemorrhage, visual disturbance, vitreous floaters, conjunctival hemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus. The most frequently reported non-ocular adverse reactions are headache, nasopharyngitis and arthralgia.
Less frequently reported, but more serious, adverse reactions include endophthalmitis, blindness, retinal detachment, retinal tear and iatrogenic traumatic cataract.

The investigational biosimilar of Lupin is also supplied as a single-use, 2-cc glass vial containing 2.3 mg of ranibizumab in 0.23 mL designed to deliver 0.05 mL of 10 mg/mL ranibizumab, by intravitreal injection. The PCT study that has been conducted with LUBT010 includes the repeated dose (4-week) intravitreal toxicity study in rabbit with 14-day recovery period.

Pre-clinical program of Lupin's biosimilar ranibizumab revealed that it is safe and well tolerated when given intravitreally. Moreover, it is also well tolerated at the site of injections. Lupin has demonstrated analytical, functional and *in vivo* nonclinical similarity to Lucentis®. Therefore, Lupin intends to take this product forward in the clinical development.

### 3.3 Rationale

Ranibizumab is a valuable treatment option for patients with neovascular (wet) AMD. The safety and tolerability of Lucentis® has been studied in various Phase 1 to 4 clinical studies. The results have demonstrated well accepted efficacy and safety profile. The reference medicinal product for this study – Lucentis® is approved and available in the market globally since 2006. Therefore, the risks are well known, and the benefits outweigh the risks for the treatment of neovascular AMD.

Ranibizumab interferes with a small protein known as VEGF that stimulates the very angiogenesis that lies at the heart of neovascular AMD. Based on sound pathological mechanism of action, ranibizumab addresses the unmet need in the treatment of neovascular (wet) AMD. However, the high costs of treatment have been a major issue of concern making

it practically unaffordable to the common people. This has made off-label anti-VEGF agent bevacizumab the preferred choice against the regulatory framework.[9]
Therefore, development of biosimilar of ranibizumab has become imperative and the need for encouragement of companies for developing biosimilars has gained importance so that the right to treatment can be equally bestowed to everyone in need. Introduction of biosimilar of ranibizumab would offer a cost-effective option for treatment of patients with neovascular AMD.

LUBT010 has been developed as an investigational biosimilar of Lucentis® and has been found to be safe and well tolerated in pre-clinical program so far (similarity has been demonstrated through quality/ analytical and PCT studies). This Phase III clinical study in patients with neovascular AMD, is a part of biosimilar development pathway and in line with regulatory requirements, to demonstrate the biosimilarity between Lucentis® and LUBT010. The indication selected is one of the major indications studied by the innovator. The biosimilar development requires a comparative similarity with reference biologic at all steps of development, thus the RMP 'Lucentis®' is the active control arm.

This study has mean change in Best Corrected Visual Acuity (BCVA) from baseline as the primary endpoint. This is a globally accepted primary end point. The methodology used to measure visual acuity is by using Early Treatment Diabetic Retinopathy Study (ETDRS) chart which has been endorsed by the Food and Drug Administration (FDA).[13] Assessment of immunogenicity is of critical importance to characterize potential differences between the biosimilar candidate and the reference medicinal product in terms of the incidence and severity of human immune responses and is considered a key component of a biosimilar's clinical development program. Since both pre-treatment and post treatment incidences of antibodies have been reported with Lucentis®, comparative immunogenicity assessment has also been included in this trial.

This study includes monthly injections of ranibizumab (LUBT010 or Lucentis®) for a treatment duration of 12 months. The US prescribing information for Lucentis® recommends monthly injections for optimal visual acuity outcomes. Studies have also suggested higher efficacy with monthly regimen as compared to PRN regimen with statistically significant difference of 2.4 letters found in favor of monthly dosing compared with PRN treatment.[9] Neovascular AMD, being a chronic progressive disease, patients are required to receive therapy for long duration. In addition, the landmark trials for ranibizumab (ANCHOR[14] MARINA[15] and HARBOR[16]) have satisfactorily evaluated the primary endpoints with 12 monthly injections. As per the MARINA trial results, more than 90% of patients in each treatment group remained in the study at 12 months, thus meeting the endpoints satisfactorily. Therefore, a study duration of 12 months with monthly injection intervals is considered appropriate for assessment of efficacy, safety, and immunogenicity in this study.

## 3.4 Risk-Benefit Assessment

Since LUBT010 has been developed as an investigational biosimilar to Lucentis®, its risk/ benefit profile is considered to be similar to that of Lucentis®. The safety and tolerability of Lucentis® have been studied in various Phase 1 to 4 clinical studies. The results have demonstrated well accepted efficacy and safety profile. The impressive results with ranibizumab are far superior to those seen with PDT or pegaptanib. Therefore, monotherapy ranibizumab has become the standard of care for patients with subfoveal CNV due to AMD regardless of type and size of lesion.[16] The reference medicinal product ranibizumab (Lucentis®) is approved and available in the market globally since 2006; therefore benefits are well proven and the risks are known for the treatment of AMD.

The risks associated with the use of RMP are summarized in the Summary of Product Characteristics[10] and Prescribing Information[11] of Lucentis®. It is advised that the injection be administered only by qualified ophthalmologists experienced in intravitreal injections with adequate aseptic precautions, prophylactic antimicrobial therapy, and monitoring for AEs. If these precautions are taken care of, Lucentis® is a valuable therapy for the treatment of AMD.

In the pre-clinical development program, LUBT010 was found to be comparable to the Lucentis® and has shown that the PCT profile is acceptable and did not reveal any significant toxicity at doses which were up to 3 times of human doses.

Since LUBT010 is an investigational biosimilar of Lucentis®, it is anticipated that the patients randomized to the LUBT010 arm will have a similar potential for benefit from treatment as those randomized to the Lucentis® arm.

### 3.4.1 Risk Assessment related to COVID-19 Pandemic

As per EMA guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic, ongoing risk assessments of the impact of the COVID-19 pandemic on the study will be performed. A risk mitigation/contingency plan is prepared for this purpose and takes into account current knowledge about COVID and mitigation of potential uncertainties.

# 4 STUDY OBJECTIVES

## 4.1 Primary Objective

To demonstrate the equivalence in efficacy of LUBT010 to Lucentis® in terms of visual acuity, in patients with neovascular Age-Related Macular Degeneration.

## 4.2 Secondary Objectives

- To assess the safety and tolerability of LUBT010 as compared to Lucentis®.
- To assess the immunogenicity of LUBT010 as compared to Lucentis®.

# 5 STUDY ENDPOINTS

## 5.1 Primary Efficacy Endpoint

Mean change in BCVA from baseline in the study eye at the end of 12 months, assessed with the ETDRS chart.

## 5.2 Secondary Endpoints

### 5.2.1 Efficacy

- Mean change in BCVA from baseline in the study eye at the end of 3 months, assessed with the ETDRS chart.
- Mean change in BCVA from baseline in the study eye at the end of 6 and 9 months, assessed with the ETDRS chart.

### 5.2.2 Safety

- Adverse Events (AE) assessment, ocular and non-ocular
- Ophthalmic examination
- Physical and systemic examination
- Vital signs
- Electrocardiogram (ECG)
- Laboratory parameters - Blood (hematology and biochemistry) and urinalysis

### 5.2.3 Immunogenicity

Proportion of patients with anti-drug antibodies at the end of 1, 3, 6, 9, and 12 months.

## 5.3 Exploratory Endpoint

- Mean change from baseline in National Eye Institute Visual Functioning Questionnaire – 25 (NEI-VFQ-25) Version 2000 (interviewer administered) scores at 3, 6, and 12 months.

# 6 INVESTIGATIONAL PLAN

## 6.1 Overall Study Design and Plan

This is a global, Phase III, double blind, randomized, controlled clinical study. The objective of the study is to compare the efficacy, safety and immunogenicity of LUBT010 to that of Lucentis® in patients with neovascular AMD.

Approximately 75 –100 sites across Europe, US, and India, having ophthalmologists who are experienced in diagnosing and treating neovascular AMD, and where adequate facilities for conduct of trial are available will be selected for the study. Study will be initiated only after receipt of regulatory and EC approval. Screening investigations on patient will be done only after signing of written informed consent. Adequate number of patients will be screened to randomize approximately 600 patients to have 558 evaluable patients in the study. (Note: Every attempt will be made to ensure at least 25% of patients enrolled are with light colored irises).

Patients will be randomized on Day 1. Total 12 injections (Lucentis® or LUBT010 0.5 mg intravitreal injection, once monthly) would be given to each patient during the study. The duration of the treatment and assessments will be 12 months during which the efficacy, safety and immunogenicity assessments will be done. The total study duration for each patient would be around 13 months. It would include up to 28 days of screening period and 12 months of treatment and assessment period.

The trial consists of following parts:

- Screening Period (maximum 28 days)
- Treatment and Assessment Period (12 months)
    - Day 1 (Randomization and first dose of ranibizumab)
    - Safety Visit: Day 2 to 9 (on any day from Day 2 to Day 9)
    - Treatment visits (± 2 days): Day 31 (second dose), and thereafter monthly for a total of 12 months (i.e. Day 61, Day 91, Day 121, Day 151, Day 181, Day 211, Day 241, Day 271, Day 301, and Day 331) followed by post-injection visit/Telephonic Follow-Up, as deemed necessary by Investigator.
    - Day 360 (± 2 days) - End of Study (EOS)

After signing the informed consent form, the patients will undergo screening assessments to confirm eligibility. These include demographics, medical and surgical history, (including ophthalmic history), weight, ECG, vital signs, physical, systemic and ophthalmic examination, and laboratory assessments (blood and urine) as given in Table 1.
Screening period will be of maximum 28 days. The eligible patients will then be randomized on Day 1 in 1:1 ratio, to receive either LUBT010 or Lucentis® as an intravitreal injection. The patients will visit the clinical facility for all 12 injections which will be administered once a month.
In a situation where the day of first dosing is different from day of randomization, all the visit days should be calculated from Day 1 (day of first dosing) rather than day of randomization.

Assessment of efficacy, safety, and immunogenicity will be done periodically during the study as given in the schedule of assessment table (Table 1).
Safety includes AE assessment (ocular and non-ocular), ophthalmic examination, and changes from baseline in vital signs, physical and systemic examination, ECG, and laboratory parameters.

## 6.2 Discussion of Study Design

This is a global, phase III, double blind, randomized controlled interventional study to be carried out in patients with neovascular AMD. The present study is designed in conformance with guidelines on biosimilar development which requires demonstration of comparable efficacy and safety between the investigational biologic LUBT010 and the reference medicinal product Lucentis®.
LUBT010 has been developed as an investigational biosimilar of Lucentis® and has been found to be safe and well tolerated in pre-clinical program so far (similarity has been demonstrated through quality/ analytical and PCT studies). Lucentis® is a biologic approved by both US FDA and EMA with a well-established efficacy and safety profile, and therefore, chosen as a comparator in the current study. Randomization and double blinding methods will be used to avoid selection and evaluation bias.

Neovascular (wet) AMD is a primary approved indication for Lucentis®; hence the patients with neovascular (wet) AMD will be enrolled in the study. The dose chosen for the study is 0.5 mg intravitreal injection once a month, which is the approved and recommended dose of Lucentis® for this indication.

Thus, to demonstrate the equivalence in efficacy and safety, this head-to-head study comparing LUBT010 with Lucentis® using double-blind, randomized controlled design is deemed most appropriate.

### 6.2.1 Choice of Study Population

Indication: Neovascular AMD was the first indication for which ranibizumab was approved. Several studies have been conducted in this population and monotherapy with ranibizumab has become the standard of care for patients with CNV due to AMD regardless, of type and size of lesion; hence, patients with Neovascular AMD as study population have been selected.

Age: Age-related macular degeneration occurs predominantly in the elderly. It is the leading cause of irreversible blindness among people who are 50 years of age or older in the developed world. Therefore, male and female patients $\geq$ 50 years with neovascular AMD have been selected for the study.

Single Eye: Only one eye will be assessed as study eye in this trial. This is in line with pivotal clinical trials of innovator's ranibizumab. However, should AMD therapies required for other (non-study) eye during the study, the same can be allowed as per section 7.1.6.

Considering these factors, the chosen study population is appropriate for the study.

### 6.2.2 Appropriateness of Measurements

The primary and secondary endpoints chosen for the study are the ones used during development of Lucentis® and well accepted by various Regulatory agencies. Similarly, other

efficacy and safety parameters proposed are also in line with the conventional endpoints used in such type of studies. In line with requirements for biosimilar development, immunogenicity has also been included in this study.

### 6.2.3 Control Group

The biosimilar development requires a comparative similarity with reference biologic at all steps of development. Accordingly, present study has reference biologic EU-approved Lucentis® as the active control arm.

### 6.2.4 Duration of Study

Neovascular AMD, being a chronic progressive disease, patients are required to receive therapy for long duration. In addition, the landmark trials for ranibizumab (ANCHOR[14], MARINA[15] and HARBOR[16]) have satisfactorily evaluated the primary endpoints with monthly injections for a period of 12 months. As per the MARINA trial results, more than 90% of patients in each treatment group remained in the study at 12 months, thus meeting the endpoints satisfactorily. Therefore, a treatment duration of 12 months is considered a relevant time period to assess the efficacy, safety, and immunogenicity in this study.

## 6.3 Schedule of Assessments

The schedule of assessments to be performed at each visit is indicated in Table 1 (Schedule of Assessment). For details, refer Section 6.3.1 given below.

### 6.3.1 Detailed Study Assessments

The objective of this clinical study is to study efficacy, safety, and immunogenicity of LUBT010 in comparison with Lucentis®.

The following assessments will be performed at each study visit:

#### 6.3.1.1 **Screening Visit** (Maximum 28 days)

Screening procedures are as follows:

- Obtain written informed consent as per regulatory requirement
- Record demographic data (age, gender, race/ethnicity)
- Record medical and surgical history (including ophthalmic history)
- Record concomitant medications/treatment.
- Vital signs assessment (temperature, Pulse, blood pressure [BP], respiratory rate [RR])
- Perform physical and systemic examination
- Record weight
- Perform ECG
- AE assessment
- Perform clinical laboratory assessment (hematology, biochemistry, and urinalysis) (and any other investigation, if deemed necessary by investigator)
- Assessment of serological tests[#] for: human immunodeficiency virus (HIV), Hepatitis B virus (HBsAg), Hepatitis C virus (HCV), and syphilis (Rapid Plasma Reagin [RPR] test).
- Follicle stimulating hormone (FSH) to be done in all females at screening.

Perform serum pregnancy test in females of childbearing potential (females who are not surgically sterile or menopausal).

- Ophthalmic Examinations[@]: Unless otherwise stated these will be done for both the eyes
  - Refraction assessment
  - BCVA by ETDRS chart*
  - Ophthalmoscopy examination (indirect dilated)
  - Slit lamp examination
  - Intraocular pressure (IOP) measurement
  - Fluorescein angiography (FA)[#]: History of sensitivity to fluorescein dye to be checked before FA
  - OCT[#]

@ Refraction and visual acuity testing should be done before pupil dilation and prior to other ophthalmic investigations. Only when the patient is eligible based on BCVA, the remaining investigations should be done. The order in which various procedures are performed may vary from clinic to clinic, provided the procedures are completed within screening period.

# The period of 28 days can be relaxed up to two months for the tests marked # considering the longevity of the results for patients who may undergo rescreening (see Section 6.4.4).

* BCVA measurements should begin in a sitting position using ETDRS chart (original Sloan letter chart or number chart) at a starting distance of 4 meters (for a subject, the same ETDRS chart used at screening should be used for all subsequent visit). A standardized ETDRS chart must be used at all participating sites to minimize the assessment discrepancy. Visual acuity measurements for each eye should be obtained by an ophthalmologist or a certified examiner.

* Testing of visual acuity will be performed before the patient's eyes are dilated and before other ophthalmic investigations like ophthalmoscopy, slit lamp, tonometry, FA or OCT if these procedures are to be carried out on the same day.

- Assess patient eligibility against inclusion and exclusion criteria.
- The eligible patients will be informed about Randomization visit and prescribed antimicrobial therapy (eg, systemic medications/ self-administer antimicrobial drops as prescribed by Investigator before and following each injection)

#### 6.3.1.2 **Treatment Period** (12 months)

##### 6.3.1.2.1 Day 1 (Randomization and Ranibizumab First Dose Administration)

Randomization should be performed within maximum of 28 days of screening.

**Day 1 (Predose)**

- Vital signs assessment
- Urine pregnancy test (in females of childbearing potential [females who are not surgically sterile or menopausal])
- Perform physical and systemic examination
- Confirmation of eligibility based on screening results and investigations done on Day 1

- Ophthalmic Examinations: Unless otherwise stated these will be done for both the eyes
  - Refraction assessment
  - BCVA using ETDRS*
  - Ophthalmoscopic examination
  - IOP measurement
  - Slit lamp examination
- Interviewer administered NEI-VFQ-25 (baseline)
- Immunogenicity (anti-drug antibody) assessment
- Record changes in concomitant medication/treatment – if any
- AE assessment
- Randomization
- Administer study medication in study eye only (if antimicrobial therapy taken as prescribed).

**Day 1 (Postdose)**

- Vital signs assessment
- IOP measurement for study eye only at 60 min (± 30 min) post injection
- Ophthalmoscopic examination in study eye only.
- Observe for at least 60 min (± 30 min) postdose (post injection)
- AE assessment
  Note: * notes of screening visit to be followed.

#### 6.3.1.2.2 Day 2 to 9

The Day 2 -9 visit can be on any day from Day 2 to Day 9.

- Vital signs assessment
- IOP measurement
- Ophthalmoscopic examination
- Slit lamp examination
- AE assessment
- Inquire if antimicrobial therapy is taken as prescribed
- Record changes in concomitant medication/treatment

#### 6.3.1.2.3 Visit Days (± 2 days): Day 31, 61, 91, 121, 151, 181, 211, 241, 271, and 301

**Pre dose**

- Vital signs assessment
- Urine pregnancy test in females of childbearing potential
- Perform physical and systemic examination
- Record ECG (only at Day 181)
- Perform clinical laboratory assessment (hematology, biochemistry and urinalysis) at Day 91, Day 181, and Day 271.
- Ophthalmic Examinations: Unless otherwise stated these will be done for both the eyes

- Refraction assessment
- BCVA using ETDRS*
- Ophthalmoscopic examination
- Slit lamp examination
- IOP measurement (Obtained pretreatment for both eyes)

- Interviewer administered NEI-VFQ-25 at Day 91 and Day 181.
- Immunogenicity (anti-drug antibody) assessment at Day 31, Day 91, Day 181, and Day 271.
- Record changes in concomitant medication/treatment
- AE assessment
- Administer study medication into study eye only (if antimicrobial therapy taken as prescribed).

**Postdose**

- Vital signs assessment
- IOP measurement (Obtained at 60 min [± 30 min]) post injection in study eye only)
- Ophthalmoscopic examination in study eye only
- Observe for at least 60 min (± 30 min) postdose (post injection)
- AE assessment

Note: * notes of screening visit to be followed.

#### 6.3.1.2.4 Post injection visit / Telephonic Safety Assessment after injection administration

A post injection visit/ telephonic safety assessment after injection administration will be done as deemed necessary by Investigator for the following:

- AE assessment
- Inquire if antimicrobial therapy is taken as prescribed
- Record changes in concomitant medication/ treatment.

#### 6.3.1.2.5 Day 331 ± 2 days (EOT)

**Day 331 (Pre dose)**

- Vital signs assessment
- Perform physical and systemic examination
- Urine pregnancy test in females of childbearing potential
- AE assessment
- Record changes in concomitant medication/treatment
- Ophthalmic Examinations: Unless otherwise stated these will be done for both the eyes
  - Refraction assessment
  - BCVA using ETDRS*
  - Ophthalmoscopic examination
  - Slit lamp examination
  - IOP measurement

- Administer study medication into study eye only (if antimicrobial therapy taken as prescribed).

**Day 331 (Post dose)**

- Vital signs assessment
- IOP measurement (Obtained at 60 min [± 30 min]) post injection in study eye only)
- Ophthalmoscopic examination (for study eye only)
- Observe for at least 60 min (± 30 min) post dose (post injection)
- AE assessment

Note: * notes of screening visit to be followed.

#### 6.3.1.2.6 Day 360 ± 2 days (EOS/Early Discontinuation)

The following procedures will be performed at Day 360 ± 2 days or at the time of withdrawal/discontinuation prior to 12 months of treatment:

- Vital signs assessment
- Perform physical and systemic examination
- Perform clinical laboratory assessment (hematology, biochemistry, and urinalysis)
- Perform Urine pregnancy test in females of childbearing potential only
- Record ECG
- AE assessment
- Record changes in concomitant medication/treatment
- Ophthalmic Examinations: Unless otherwise stated these will be done for both the eyes
    - Refraction assessment
    - BCVA using ETDRS*
    - Ophthalmoscopic examination
    - Slit lamp examination
    - IOP measurement
- Immunogenicity (anti-drug antibody) assessment
- Interviewer administered NEI-VFQ-25

Note: * notes of screening visit to be followed.

Post EOS visit or discontinued patients (anytime during study) may be shifted to appropriate standard therapy by the Investigator depending on the disease condition.

## 6.4 Selection of Study Population

### 6.4.1 Inclusion Criteria

Patients satisfying all of the following criteria will be included in the study:

1. Ambulatory male or female participants with age ≥ 50 years at the time of screening who are capable of understanding and giving written informed consent.

2. Primary or recurrent (anti-VEGF naïve) active CNV[@] lesions involving the foveal center secondary to AMD in any one of the eyes.
3. BCVA in the study eye, using ETDRS testing, between 20/40 and 20/200 (Snellen equivalent), both inclusive, before pupil dilation.
4. Willingness and ability to undertake all scheduled visits and assessments.
5. Females, who are of non-child bearing potential (surgically sterile or menopausal), OR, if of child bearing potential using effective birth control measures and non-pregnant and non-lactating during the study and 3 months after the last dose (Refer Section 2 - Definition of Terms).

[@]*Active CNV is defined as any leakage detected on FA*

### 6.4.2 Exclusion Criteria

Patients who meet any of the following criteria should be disqualified from entering the study:

1. Known hypersensitivity to ranibizumab or any of the components of study medication.
2. Known history of allergy to fluorescein dye.
3. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye as assessed by FA (confirmed by independent central reading center).
4. Subretinal hemorrhage in the study eye that involves the center of the fovea, the size of the hemorrhage is either ≥ 50% of the total lesion area or ≥ 1-disc area in size (confirmed by independent central reading center).
5. Total lesion area ≥ 12.0-disc areas (DA) in size (including blood, scars, and neovascularization) as assessed by FA in the study eye (confirmed by independent central reading center).
6. History of vitrectomy, submacular surgery, or other surgical intervention for AMD in the study eye.
7. Employees of clinical study sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who are legally institutionalized.
8. Any other pathology involving the CNV lesion like retro-foveolar atrophy or permanent structural damage to fovea or fibrosis/ hemorrhage involving fovea > 50% of lesion area of study eye that can affect the efficacy of drug.
9. Vitreous hemorrhage or history of rhegmatogenous retinal detachment, retinal pigment epithelial tears or rips involving the macula or macular hole (stage 1 to 4) in the study eye as assessed by FA (confirmed by independent central reading center).
10. Uncontrolled glaucoma as evident by progressive damage to optic nerve or visual fields despite optimum therapy; or steroid-induced glaucoma with continued use of steroids that requires IOP-lowering treatment.
11. History of serious complications following surgery in the study eye within 1 year prior to randomization.
12. Previous treatment with intravenous or intravitreal anti-VEGF agents such as Bevacizumab, Ranibizumab, Aflibercept, Pegaptanib, Brolucizumab in either of the eyes.
13. Previous external beam radiation or any laser therapy photocoagulation/ thermal laser thermotherapy/verteporfin photodynamic therapy (PDT) involving the foveal center in the study eye within 5 years prior to randomization.

14. Previous treatment with verteporfin photodynamic therapy (PDT), thermal laser, transpupillary thermotherapy (except subfoveal) in the study eye or use of protein kinase C inhibitors within 3 months prior to randomization.
15. Previous treatment with intravitreal steroids (e.g., triamcinolone, anecortave acetate) in the study eye within 3 months prior to randomization.
16. Previous treatment with intravitreal steroid implant (like Ozurdex®) within 6 months prior to randomization.
17. Concurrent use of systemic anti-VEGF agents.
18. Intraocular surgery (including cataract surgery) in the study eye within 3 months prior to randomization.
19. Concurrent treatment with an investigational drug or device in the non-study eye.
20. Previous participation in any studies of investigational drugs within 30 days or as prescribed in that study (whichever is later) preceding the initial study treatment.
21. Patients who have DME and/or background or proliferative retinopathy will be excluded. Likewise, any with significant posterior subcapsular cataract (PSC) should be excluded
22. CNV in the study eye due to causes other than AMD such as histoplasmosis, trauma, or pathological myopia etc. or CNV lesion not likely to respond to ranibizumab.
23. Active or ongoing ocular infection (e.g. infectious conjunctivitis, keratitis, scleritis, or endophthalmitis) or severe inflammation in either of the eyes.
24. Any concurrent intraocular condition in the study eye that could either require medical or surgical intervention during the 12 month study period or that could contribute to a loss (of at least 2 Snellen equivalent lines) of BCVA over the 12 months study period (e.g. progressive retinal disease or retinal pathology, cataract, glaucoma, uveitis, previous corneal transplant, the refractive error more than -8 diopters of myopia etc.). The decision regarding exclusion is to be based on the opinion of the Investigator.
25. Any patient with cloudy media from any cause that prevents adequate visualization of the fundus with indirect ophthalmoscopy should be excluded.
26. Patients with seropositivity for hepatitis B, hepatitis C, HIV antibody, syphilis tests or any immunodeficiency and/or immunosuppressive disease or active systemic infection.
27. History or presence of concurrent systemic diseases or dysfunctions ***requiring significant medical/ surgical intervention during study period*** that might affect interpretation of the results or contraindicates the use of ranibizumab or render the patient at high risk for treatment complications based on the Investigator's judgment ***such as***:
    - Cardiovascular disease (e.g. stroke, myocardial infarction), uncontrolled respiratory, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic (e.g. optic neuropathy), metabolic, pulmonary, autoimmune disease or psychiatric disease based on previous history and relevant reports of clinical examination, laboratory tests, or ECG etc.

### 6.4.3 Withdrawal and Discontinuation of Patients

Patients may discontinue the study at any time without any penalty or loss of benefits to which the patient is otherwise entitled. For all patients withdrawn from the study, efforts will be made to ascertain the reason for withdrawal.

A withdrawn patient is one who meets any of the following withdrawal criteria stated below and whose study participation is discontinued. The reasons for patient withdrawal will be recorded in the electronic case report form (eCRF).
In case of early discontinuations/ premature termination of the study all EOS investigations should be done on the day of termination as far as possible.

**Criteria for Withdrawal from Study:**

- The patient is not willing to continue participation in the study (withdraws consent).
- Lost to follow-up

**General Criteria for Treatment Discontinuation**

- The patient needs emergency treatment or is unable to continue participation in the trial due to the exacerbation of their symptoms.
- Inability of patient to comply with the Protocol for any reason.
- The patient becomes pregnant during the study period.
- In the opinion of the Investigator or sub-investigator, the patient should be discontinued due to AEs (including progressing complications) or safety reasons.
- Other reasons due to which the patient should be discontinued, in the opinion of the Investigator or sub-investigator.

**Ocular Criteria:**

**Treatment Discontinuation:**

Treatment should be discontinued in patients with rhegmatogenous retinal detachment or stage 1 to 4 macular holes.

**Dose Withholding Criteria:**

The dose should be withheld/postponed, and treatment should not be resumed earlier than the next scheduled treatment in the event of:

- a decrease in best-corrected visual acuity (BCVA) of ≥30 letters in study eye compared with the last assessment of visual acuity;
- an IOP of ≥30 mmHg before dosing;
- a retinal break;
- a subretinal hemorrhage involving the center of the fovea, or, if the size of the hemorrhage is ≥50%, of the total lesion area;
- performed or planned intraocular surgery within the previous or next 28 days

Based on OCT result, should the investigator decide to withhold an injection for potential safety concern, a pro-re-nata (PRN) or treat-and-extend regimen can be used.

Any conditions given above or any other significant medical conditions (for example severe local or systemic infection or inflammation in either of the eyes) that can significantly affect efficacy or safety, in opinion of Investigator, will be discussed on case to case basis with the Sponsor and the patient can be withdrawn from the study, if justified.

The treatment options will be discussed with all patients who have discontinued or completed study (EOS) and the patients will be continued on/ shifted to appropriate standard therapy by the Investigator depending on the disease condition.

### 6.4.4 Rescreening of Patients

Rescreening of a previously screen failed patient will be allowed for patients determined as screen failure due to inclusion and/or exclusion criteria that could transiently change and do not compromise the patient's safety. Rescreens may occur until the sites are open for recruitment. **Only one rescreen is allowed per patient**.

When a rescreen is authorized by the Sponsor or designee, patient is to be consented again and all screening procedures should be completed (for serology, FA and OCT please refer to Section 6.3.1.1).

Patients who discontinue the study after randomization or after receiving study medication are not eligible for rescreening.

### 6.4.5 Other Patient Restrictions

Patients may not participate in another clinical study that involves an investigational product (IP) during this study.

Females patient currently pregnant or breast feeding or planning to conceive are not allowed to be included in the study. Female patients should refrain from becoming pregnant during the study period and should use effective contraception during the study and 3 months after the last dose of study drug.

For concomitant medications/treatments which are restricted during the study, please see Section 7.1.6.

### 6.4.6 Early Termination of Study/ Site

This study may be terminated at any time by the Sponsor if, the Investigator does not adhere to the protocol, non-performance or inability to follow the advices by the regulatory authorities of the country for global study, or in the Sponsor's judgment there are no further benefits to be achieved from the study or due to non-viability of the study on commercial grounds. In this event, the Sponsor will inform about the decision along with reason to the study Investigators, Institutions, ECs and all applicable regulatory authorities for the termination of study.

# 7 TREATMENT OF PATIENTS AND INVESTIGATIONAL PRODUCT MANAGEMENT

## 7.1 Treatment of Patients

### 7.1.1 Dosages & Treatment Regimen

Investigational products (LUBT010 & Lucentis®) will be administered as intravitreal injection in the study eye. All the patients will be randomized to one of the two arms viz. LUBT010 or Lucentis® arm, as per Table 2.

**Table 2: Doses and Treatment Regimen**

| Treatment Arm | Dose | Route | Duration & Frequency |
|---|---|---|---|
| **LUBT010** | 0.5 mg | Intravitreal injection in the study eye of patients | Total 12 injections per patient; Once monthly (approximately 28 days) |
| **Lucentis®** | 0.5 mg | Intravitreal injection in the study eye of patients | Total 12 injections per patient; Once monthly (approximately 28 days) |

### 7.1.2 Precautions while Administering Investigational Product

Investigational products (LUBT010 and Lucentis®) should be administered only by qualified ophthalmologists experienced in intravitreal injections. The interval between two doses should not be less than 28 days.

Before treatment, the patient should be instructed to administer antimicrobial therapy (as prescribed by Investigator before and following each injection). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to intravitreal injection.

The intravitreal injection procedure should be carried out under controlled aseptic conditions. Adequate anesthesia and a broad-spectrum antimicrobial should be given prior to the injection.

As with all medicinal products for parenteral use, IP should be inspected visually prior to administration.

Prior to and 60 min (± 30 min) following the intravitreal injection, patients should be monitored for elevation in IOP using tonometry. Monitoring may also consist of a check for perfusion of the optic nerve head (Ophthalmoscopy) after the injection. Patients should also be monitored for and instructed to report without delay any symptoms suggestive of endophthalmitis following the injection. Details pertaining to preparation for administration of Investigational product is provided in Appendix A.

### 7.1.3 Randomization of Study Treatments

The treatment arm (test or reference) for each patient during the study will be assigned according to randomization list. This randomization list will be prepared reviewed and finalized in a blinded manner and will not be accessible to the study team involved in the study conduct. The treatment will be assigned at the time of randomization, after confirming patient's

eligibility. Patients will be randomized in a 1:1 ratio to either LUBT010 or Lucentis®. Patients who qualify for study randomization will have a unique randomization number. Randomization will be stratified by iris color (light colored, not light colored) to maintain treatment balance within strata. Randomization block size will be specified in the randomization plan and will not be shared with investigators. After completion of required number (600 patients), some patients who qualify in screening may not be enrolled in the study.

### 7.1.4 Blinding of Study Treatment

This study will be performed in a double-blind manner. In order to maintain the double-blind status of the study, packaging of LUBT010 will have similar appearance to the Lucentis®. Investigator/ other members of staff involved in the study and patients will remain blinded to the treatment arm during the study.

#### 7.1.4.1 Breaking the Blind for Safety Reason

Randomization codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s)/site, if required, as mentioned below.

The randomization code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment armor to meet regulatory requirements (e.g., in the case of SAE or death). In this case individual randomization codes, indicating the treatment arm for each randomized patient, can be made available to the Investigator(s).

If possible, there should be a discussion among the Investigator and Lupin study team and/ or the medical expert prior to breaking the code. If the blind is broken, the date, time, and reason for unblinding must be recorded. If the treatment information is unblinded, the Investigator should document and report the action to Lupin. Patients will immediately be discontinued from the study by the Investigator and the EOS visit assessments will be performed.

#### 7.1.4.2 Breaking the Blind for Regulatory Authorities

If requested by regulatory agency, the blind can be broken and the unblinded safety information will be provided to the regulatory authority. In such cases, the patients can continue participation in the study.

### 7.1.5 Patient Compliance

For this study-purpose the per protocol compliance to study medication will be defined as all those randomized patients who receive all the 12 intravitreal injections of 0.05 mL of 10 mg/mL ranibizumab in the study eye.

### 7.1.6 Concomitant Therapy

**Prohibited Medications:** Other therapies for the treatment of AMD, including but not limited to Verteporfin photodynamic therapy, Pegaptanib, Bevacizumab, Aflibercept or Brolucizumab will not be allowed in the study eye during the study. Anti-VEGF therapy, other than ranibizumab (approved innovator product) for treatment of exudative AMD in the respective country, will not be allowed in the non-study eye during the study. Other biologics will not be allowed during the study. Any other experimental therapy for treatment of AMD will not be allowed in study eye or non-study eye during the study.

**Allowable Medications:** Any other medications/ treatments required by the patient and not expected to interfere with study assessments will be allowed on a case-by-case basis and as deemed appropriate by the Investigator. Therapies like thermal laser and verteporfin PDT for AMD can be allowed in the non-study eye at the discretion of the Investigator. Anti-VEGF therapy [ranibizumab (approved innovator product) for treatment of exudative AMD in the respective country] can be administered in non-study eye as needed when deemed to be clinically justified in the opinion of the Investigator. Supplementation with antioxidant & minerals (non-investigational treatments) (e.g. lutein zeaxanthine or beta carotene, Vitamin C, E, and Zinc) can be allowed[17].

## 7.2 IP MANAGEMENT

### 7.2.1 IP Dosage Form and Strength

LUBT010/Lucentis® for Intravitreal injection is supplied as single-use vial designed to deliver 0.05 mL of 10 mg/mL ranibizumab. The details of the study medications are given in Table 3.

**Table 3: IP Details**

| Study Medication | Dosage Form and Strength | Sourced from |
|---|---|---|
| LUBT010 | Supplied as single-use, 2-cc glass vial containing 2.3 mg of ranibizumab in 0.23 mL solution designed to deliver 0.05 mL of 10 mg/mL ranibizumab, by intravitreal injection. | Lupin Limited (Biotech Division), Gat No: 1156, Village Ghotawade, Taluka Mulshi, Pune, Maharashtra, India– 412115 |
| EU-approved Lucentis® | Supplied as single-use, 2-cc glass vial containing 2.3 mg of ranibizumab in 0.23 mL solution designed to deliver 0.05 mL of 10 mg/mL ranibizumab, by intravitreal injection. | (Marketing Authorization Holder in UK)<br>Novartis Europharm Limited<br>Vista Building<br>Elm Park, Merrion Road<br>Dublin 4<br>Ireland. |

### 7.2.2 IP Packaging and Labelling

A single-use, 2-cc glass vial (LUBT010 or Lucentis®) will be packaged individually in cartons along with syringes and needles. The packs will be labeled as per regulatory requirements. Each pack will have unique identification number.

Each patient will be assigned a randomization number and IP pack containing either LUBT010 or Lucentis® will be dispensed.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The label text will be translated into local language. The labels shall contain appropriate information as per the local regulatory requirements including but not limited to product content and strength, batch No, manufacture date, retest/ expiry date, storage information, route of administration, statements like “For Clinical Trial Purpose Only”.

### 7.2.3 Storage

Investigational product (Ranibizumab) injection should be stored under refrigeration at 2º-8ºC (36º-46ºF) at all times. The product should be kept in the original carton to protect from light

until the time of use. Do Not Freeze. Prior to use, the unopened vial may be kept at room temperature (25°C) for up to 24 hrs. Do not use beyond the expiry date which is stated on the carton/vial. Do not use any pack if it is damaged. IP vials should be used once only, and any unused portion left in the vials should not be considered for use.

### 7.3 IP Supply, Handling and Accountability

The Sponsor/ designee will arrange for the supply, handling, and management of IPs. The Sponsor/ designee will supply sufficient quantity of IPs, for administration to randomized patients at each site. Blinded IP will be shipped under appropriate storage conditions to the Investigator sites.
The designated study personnel must take the responsibility to keep a record of the IP management.
Sites will receive IP with appropriate documents and store according to the storage requirements. Adequate records of IP for receipt, accountability, usage and disposal, or return to Sponsor will be maintained at respective Investigator site. Investigational product will be administered to eligible patients according to randomization schedule.

Pharmacist/ designated study personnel will dispense the IP for administration. The unused IP will be kept in their original containers. The sites will return any unused IP to the Sponsor or destroy on site (as mutually agreed between Sponsor and sites), once the site's monitor has reviewed and confirmed drug accountability, or at the end of the study.

Used IP vials should also be kept in the original packing and this should also be returned/ destroyed on site (as mutually agreed) to Sponsor after confirmed drug accountability by site monitor.

The IPs should not be used for purposes other than those conforming to this protocol.

# 8 ASSESSMENT OF EFFICACY

## 8.1 Efficacy Endpoints

**Primary Efficacy Endpoint:**

Mean change in BCVA from baseline in the study eye at the end of 12 months, assessed with the ETDRS chart.

**Secondary Efficacy Endpoints:**

- Mean change in BCVA from baseline in the study eye at the end of 3 months, assessed with the ETDRS chart.
- Mean change in BCVA from baseline in the study eye at the end of 6 and 9 months, assessed with the ETDRS chart.

**Exploratory Endpoint:**

- Mean change from baseline in NEI-VFQ-25 Version 2000 (interviewer administered) scores at of 3, 6, and 12 months.

## 8.2 Efficacy Variables

Mean change in BCVA from baseline in the study eye by ETDRS chart will be measured as primary and secondary endpoints. BCVA is measured by the number of letters a patient could correctly read on an eye chart; hence an increased score indicates improvement in acuity.

For this study the ETDRS chart (including original Sloan letter chart or number chart) will be used for visual acuity measurement. Standard procedures will be followed for ETDRS testing across sites. The details of the testing procedures will be described in a separate procedures' manual. It is must that testing is done prior to dilating eyes with refraction error corrected with lenses. The ETDRS testing will be standardized and made uniform across sites.

The NEI-VFQ-25 Version 2000 will be administered by the interviewer at baseline (Day 1), 3, 6, and 12 months, which is a measure of subjective response and compliments the objective findings of BCVA.

# 9 ASSESSMENT OF SAFETY

Following safety parameters will be assessed,

- AE assessment, ocular and non-ocular (as per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE V5])
- Ophthalmic examination
- Physical and systemic examination
- Vital signs
- ECGs
- Laboratory parameters: Blood (hematology and biochemistry) and urinalysis

## 9.1 Adverse Events

### 9.1.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that staff involved in the study is familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

#### 9.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign, symptom, or disease (including intercurrent illness), deterioration of a pre-existing illness, accident, any suspected drug reaction, or a clinically relevant change of laboratory values temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product and/or study treatment.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or worsens in severity after at least one dose of study drug has been administered.

See Section 9.7 below for the instances where a pregnancy should be reported as an AE.

#### 9.1.1.2 Serious Adverse Event

An SAE is defined as, any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  An AE or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of hospitalization
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Consists of any other medically important condition.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.'

### 9.1.2 Recording and Collection of Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived from spontaneous, unsolicited reports of patients, by observation, and by routine open questions.

AE reporting will extend from date of informed consent until completion of the final visit (EOS). Any ongoing AE at EOS visit (Day 360 ± 2 days) should be followed until the outcome is evident and resolved, clinically stabilized or a plausible explanation has been found.

Pre-existing diseases including deranged laboratory values (before participating in the study) are not considered to be AEs, unless the disease worsens during the study period. Concomitant diseases detected during screening or prior to randomization will be recorded in the medical history eCRF.

Signs and symptoms clearly associated with the disease under study (including symptoms of disease progression) should be reported as AEs if they are newly emergent (i.e., findings not previously observed in the patients), or are determined by the Investigator as severe or a worsening, or if the Investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug.

Abnormal laboratory values/ ECGs/ vital signs/ ophthalmic/ physical &systemic examination should be reported as AEs only if the Investigator considers the abnormality as clinically relevant or significant or believes that the abnormality should be reported as an AE.

Any dose (and associated symptoms) given to the patient that exceeds the dose prescribed to the patient has, at a minimum, to be recorded as a non-serious AE in the patient file and eCRF. Any case of overdose leading to an AE or SAE should be reported to Medical Monitor according to reporting requirements. In case of an accidental overdose, the patient should be monitored by the Investigator for any adverse clinical events including IOP, as deemed necessary by the Investigator.

After completion of all scheduled visit assessments, the Investigator must document any AEs arising from these assessments. In case of an SAE, the Investigator must also complete an SAE report form and report it to safety contact, as described in Section 9.1.3.3.

All AEs will be recorded in eCRF regardless of the causal relationship to the study drug.

All AE records should contain AE term/ AE diagnosis, date of onset, severity, relationship to the study drug, outcome, date of recovery or outcome, action taken with respect to study drug, action taken with AE, AE leading to discontinuation of patient from study, and whether the event is classified as serious.

The categorization of action taken with IP, outcome and action taken for AE is described below:

| Categories of Actions Taken with IP | Categories of Outcome* | Categories of action taken for AE |
|---|---|---|
| • Dose Delayed<br>• Drug withdrawn temporarily<br>• Drug withdrawn permanently<br>• Unknown<br>• Not applicable | • Recovered/Resolved<br>• Recovered/Resolved with sequelae<br>• Recovering/Resolving<br>• Not Recovered<br>• Fatal<br>• Unknown | • None<br>• Medication<br>• Hospitalization<br>• Non-drug treatment<br>• Patient withdrawn<br>• Other |
| *If there is more than one AE, only the AE leading to death will be attributed with a fatal outcome. | | |

In cases where multiple symptoms and signs can be described as one diagnosis (disease), the name of the diagnosis is reported as the name of the AE.
For example, running nose, cough, and sore throat: The 3 symptoms can be described as a series of symptoms of "common cold"
⇒ Common Cold or Upper Respiratory Tract Infection

The Investigator must continue to follow-up the patient with all AEs regardless of the causal relationship to the study drug until the AE has resolved or until the condition stabilizes to an acceptable level or is determined to pose no issue, or until follow-up is no longer feasible.

### 9.1.3 Evaluation of Adverse Events

Each AE is evaluated depending on the following categories by the Investigator.

#### 9.1.3.1 Definition of severity of an AE

Wherever possible, all observed AEs will be graded using the CTCAE version 5.0. The severity of the AE shall be classified using the following grading.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.).
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care (bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden).
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to an AE.
Semicolon (;) indicates “or”.

Record the maximum intensity for AE occurring frequently than once a day. If the intensity category changes over a number of days, then those changes should be recorded as a new AE with the onset date of the new intensity.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.1.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

#### 9.1.3.2 Relationship to the Study Drug

The assessment of the relationship of an AE to the administration of study drug is based on the presence or absence of a "reasonable possibility" that investigational drug has caused the AE. An AE is considered to be "related" to the study medication if a causal relationship between the IP and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out). An AE related to the study drug is referred to as an adverse drug reaction (ADR).

The expression "reasonable causal relationship" is meant to convey that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline) based on relationship to time of onset and drug administration, temporary withdrawal, not attributable to any other drug or condition, dechallenge and rechallenge information as available.

The causal relationship between an AE and the study drug will be defined as below:

**Not Related:** When the AE is definitely caused by the patient's clinical state, or the study procedure/ conditions or other concomitant drugs.

**Unlikely Related:** When the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.

**Possibly Related**: When the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/ conditions.

**Related**: When the AE follows a reasonable temporal sequence from the time of drug administration, abates upon discontinuation of the drug and reappears when the drug is reintroduced.

In final evaluation for reporting, the relationship will be converted into "Binary Determination". 'Not Related' and 'Unlikely Related' will be clubbed into "Not Related" and 'Possibly Related' and 'Related' will be clubbed into "Related" for final reporting purpose.

#### 9.1.3.3 Reporting of Serious Adverse Events

All SAEs occurring after the time of informed consent until the final visit (Day 360 visit) must be reported.

All SAEs should be reported by the Investigator to the Safety Contact via Email (at clinicalsafety@lupin.com) or telephone within 24 hours, regardless of the causal relationship with the IPs (following knowledge of the SAE). After receiving reports of the SAEs, the Safety Contact should communicate with the Investigator to get additional information for evaluation of SAEs.

The Investigator is responsible for reporting SAE (initial report, analyzed report as well as follow-up information) to the Ethics Committee (EC) and/or applicable regulatory authority as per applicable local regulatory requirements of participant countries. All SAEs shall be reported by Investigator/ Sponsor/ Sponsor designee as per applicable regulatory requirements.

**The Details of Safety Contact:**

#### 9.1.3.4 Follow – Up of Serious Adverse Events

The Investigator must continue to follow the patient until the SAE has resolved or until the condition stabilizes to an acceptable level or is determined to pose no issue, or until follow-up is no longer feasible. Any ongoing SAE at EOS visit (Day 360 ± 2 days) should be followed until the outcome is evident and resolved, clinically stabilized or a plausible explanation has been found.

#### 9.1.3.5 Suspected Unexpected Serious Adverse Reactions

An SAE that is also an unexpected ADR is called a Suspected Unexpected Serious Adverse Drug Reaction (SUSAR). Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the recent IB.

Suspected Unexpected Serious Adverse Drug Reactions will be reported in compliance with regulatory reporting requirements of participating countries. The details of reporting of SAE, significant AEs and SUSARs will be captured in the Safety Monitoring Plan (SMP).

### 9.1.4 Ocular AEs

#### 9.1.4.1 Worsening of Symptoms and Signs of Choroidal Neovascularization

Worsening of symptoms and signs of CNV should be recorded as an AE or SAE only if judged by the Investigator to have unexpectedly worsened in severity and/or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of CNV, it is important to convey why the development was unexpected. For significant Ophthalmic AEs reportable as SAEs refer the criteria below (Section 9.1.4.2).

Developing symptoms and signs that are consistent with the natural history of CNV secondary to AMD is not considered a reportable adverse event in this study.

For example, moderate loss of visual acuity over time, expansion of the size of the lesion, and increased intraretinal or subretinal fluid are common developments associated with AMD. Such information is recorded in the medical history but are not reportable AEs.

#### 9.1.4.2 Vision Threatening Serious Adverse Events

An AE is considered to be vision-threatening and is a reportable SAE, if it meets one or more of the following criteria:

- Rhegmatogenous retinal detachment or stage 1 to 4 macular holes.
- It requires surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- Any ophthalmic symptom/ eye disorder other than the above that has sight threatening consequences, requiring urgent intervention e.g. blindness in the affected eye.

### 9.1.5 Non-Ocular AEs due to VEGF inhibition

#### 9.1.5.1 Arterial Thromboembolic events

Arterial thromboembolic events like myocardial infarction, stroke should be recorded as AEs/SAEs as applicable, as there is a theoretical risk of these events following intravitreal use of VEGF inhibitors.

## 9.2 Ophthalmic Examination

Ophthalmic examinations will be done on screening and after screening according to the schedule of procedures described in Table 1.

## 9.3 Physical and Systemic Examination

A physical and systemic examination will be performed at the time of screening and after screening according to the schedule of procedures described in Table 1.

Physical examinations will include, but are not limited to, the below items:

General findings, HEENT exam (head, eyes, ears, nose, and throat), assessment of respiratory, cardiovascular, gastrointestinal, nervous, musculoskeletal, and renal/ urinary systems, lymph nodes, and dermatologic examination (including skin appendages) and other findings/ physical conditions of note. Any abnormal findings will be evaluated for clinical significance.

## 9.4 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, and body temperature will be measured at screening and after screening according to the Schedule of Assessment described in Table 1. Any abnormal findings will be evaluated for clinical significance.

## 9.5 Electrocardiogram Assessments

A 12-lead ECG will be performed at screening and after screening according to the Schedule of Assessment described in Table 1. It will be recorded by qualified personnel after the patient has been resting in the supine position for at least 3 min. Any abnormal findings will be evaluated for clinical significance.

## 9.6 Clinical Laboratory Examinations

Hematology tests, biochemistry tests including serological test (HIV, HBV, HCV, and syphilis) and urine analysis tests for safety assessment will be performed at screening and after screening according to the Schedule of Assessment described in Table 1.
The list of tests for safety laboratory assessment is shown in Table 4.

Urine Pregnancy test for females of childbearing potential will be performed at Day 1, prior to each dosing, and at EOS. Urine pregnancy test should be performed by the female patients themselves and the results reported to site during the visit.
Serum pregnancy test for females of childbearing potential will be performed at screening.
Additional tests may be performed at any time during the trial as determined necessary by the investigator or if required by local regulations.

### 9.6.1 Central Laboratory Samples

Sample collection and handling for laboratory tests will be conducted in accordance with the laboratory manuals and collected samples will be sent to the central laboratory. Not more than 280 mL of blood per patient will be collected during this study for planned study assessments (until EOS).

**Table 4: Clinical Laboratory**

| **Hematology** | **Biochemistry** | **Urinalysis** | **Serology** |
|---|---|---|---|
| Hematocrit<br>Hemoglobin<br>Platelet count<br>Red blood cell count<br>White blood cell count<br>Differential white blood cell count:<br>Neutrophils<br>Basophils<br>Eosinophils<br>Lymphocytes<br>Monocytes | Albumin<br>Globulin<br>Total protein<br>Alkaline phosphatase<br>ALT<br>AST<br>Bilirubin (total, Direct & Indirect)<br>BUN<br>Urea<br>Uric Acid<br>Creatinine<br>Random Glucose<br>Serum pregnancy*<br>FSH** | **Routine Examination**<br>Color<br>Appearance<br>pH<br>Urobilinogen<br>Occult blood<br>Glucose<br>Protein<br>Ketone<br>Specific gravity<br><br>**Microscopic Examination *(if abnormality is suspected)***<br>Red Blood Cells<br>Pus cells<br>Crystals<br>Cast<br>Bacteria<br>Yeast<br>Other | HIV<br>HBV (HBsAg)<br>HCV<br>Syphilis (RPR)[#] |
| *Serum pregnancy test will be done in females of childbearing potential.<br>**Follicle stimulating hormone (FSH) (in all females at screening visit).<br># Additional confirmatory test may be performed in RPR reactive cases, due to suspected false positivity.<br>Note: Urine pregnancy test (UPT) to be performed by the female patients themselves and the results reported to site. However, it can be repeated anytime in local/ central laboratory when pregnancy is suspected in any female patient. | | | |

Any clinical test results outside the reference value range will be evaluated for clinical significance. After dosing, laboratory abnormalities considered by the Investigator to have worsened compared to that prior to dosing will be recorded as AEs.

## 9.7 Pregnancy

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.
Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.
If a pregnancy or a positive pregnancy test is reported for a patient during study participation, the study drug must be immediately discontinued.
Pregnancies occurring during the study until EOS must be reported. All pregnancies must be reported to the Sponsor within 24 hours after becoming aware of the pregnancy, using the initial pregnancy report form. The Investigator should counsel the patient; discuss the risks of continuing with the pregnancy and possible effects on the fetus. The Investigator must follow-up and document the course and outcome of all pregnancies, even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor on the pregnancy outcome report form within 30 days after he/she becomes aware of the outcome.

Any SAE that occurs during a pregnancy must be recorded on the SAE report form (e.g. maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defects) and reported in accordance with the procedure for reporting of SAEs.

# 10 ASSESSMENT OF IMMUNOGENICITY

## 10.1 Anti-Drug Antibodies

Immunogenicity will be assessed in patients on Day 1 (pre-dose) and thereafter as per Table 1. Samples for immunogenicity will be collected prior to dosing. An appropriate and validated method will be used for assessment of anti-drug antibodies.

Note: A tiered approach will be followed for assessing antibody formation in response to IP administration. All samples will be screened for occurrence of binding antibodies. Samples that test positive will be subjected to a confirmatory assay. Samples that are positive on confirmatory assay will further be tested for assessing the titer and neutralizing potential.

### 10.1.1 Collection, Handling, and Analysis of Immunogenicity Samples

Blood samples will be collected using a blood collection tube by venipuncture.

Anti-drug antibodies will be analyzed using a validated method, at a laboratory designated for analysis of immunogenicity samples.

The sample handling, transportation, storage, and processing of will be carried out according to Laboratory Manual.

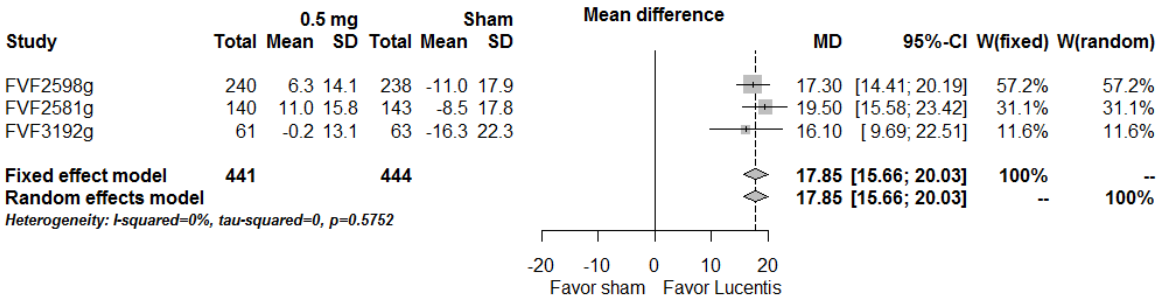
# 11 STATISTICAL EVALUATION

## 11.1 Sample Size and Power

**Sample Size for Change from Baseline in BCVA at Month 12 (Primary Endpoint)**

In order to determine the margin for equivalence, a meta-analysis based on current literature in AMD patients was performed. Data included were data from the 0.5 mg ranibizumab and the SHAM treatment groups. Studies included were in the original regulatory filing. Change from baseline to Month 12 of BCVA was used as the endpoint. A mean difference of 17.9 letters [95% CI 15.7-20.0] was found. Heterogeneity was assessed and was not found to be statistically significant (p=0.5752), and hence the fixed-effect model was used to construct the confidence interval. Based on a lower confidence bound of 15.7 letters, an equivalence margin of 4 letters preserved 74.5% of the treatment effect. The pooled standard deviation (SD) from the ranibizumab arms is 14.5 letters.

**Figure 2: Meta-Analysis**




A sample size of 558 evaluable patients allocated in 1:1 ratio (279 per treatment) at (two-sided) 5% level of significance and 80% power will be required to test the therapeutic equivalence between Lupin's LUBT010 verses Lucentis® at equivalence margin of 4 letters and SD of 14.5 letters.

Sample Size

Assuming a dropout rate of 7%, 600 patients will be randomized so as get approximately 558 evaluable patients in a 1:1 ratio between the two treatment arms (279 in each arm) to yield 80% power for the mean change from baseline in BCVA at the end of 12 months.

## 11.2 Statistical Methods

This section describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses will be provided in a Statistical Analysis Plan (SAP) as applicable.

Continuous variables will be presented in summary statistics of number of patients (n), mean, SD, median, minimum and maximum by appropriate group and time point. Categorical variables will be described using the frequency count of the events, and the number and proportion of responding patients.

The study being conducted at multiple sites, the data collected from individual sites will be pooled for analysis. Detailed listings will be produced for all relevant efficacy, safety, and immunogenicity data by treatment and by visits wherever applicable.
Detailed methodology on summary and statistical analysis of the data collected in this study will be provided in the SAP which will be finalized prior to the database lock.

### 11.2.1 Significance Level and Confidence Interval

All statistical tests will be two-sided and evaluated at a 5% level of significance.

### 11.2.2 Criteria for Equivalence

Equivalence will be determined based on the change from baseline in BCVA at Month 12. An equivalence margin of 4 letters will be used. If the 90%[#] (2-sided) confidence interval for the difference in means in change from baseline at month 12 is wholly within the equivalence margin (−4, 4), then the null hypothesis

$$H_0: \mu_1-\mu_2 \leq -4 \text{ or } \mu_1-\mu_2 \geq 4$$

will be rejected in favor of the alternative hypothesis

$$H_A: |\mu_1-\mu_2| < 4,$$

where $\mu_1$ represents the population mean change from baseline for patients treated with LUBT010, and $\mu_2$ represents the population mean change from baseline for patients treated with Lucentis®. ([#] As generally required by US Food and Drug Administration [FDA])

Similar methodology will be used with 95%[##] CI for difference. Thus, if 95% (2-sided) confidence interval, lies wholly within the equivalence margin (-4, 4), then the null hypothesis will be rejected. ([##] As generally required by the European Medicines Agency [EMA].)

## 11.3 Handling of Missing Data

There are many possible reasons for missing data (eg, patient refusal to continue in the study, treatment failures and successes, adverse events etc.), not all of which are related to the IP. Different degrees of data incompleteness can occur i.e. measurements may be available only at baseline or may be missed for one or several follow-up assessments. Such missing data will be handled by using appropriate methods. These methodologies will be described in detail in the SAP.

## 11.4 Patient Disposition

A detailed description of the patient disposition will be provided in the clinical study report. It will include the number of patients screened, randomized, completed, as well as the number of dropouts, with reasons for discontinuation and major protocol deviations. All patients entered in the study will be accounted for this.

## 11.5 Baseline and Demographic Characteristics

Categorical data will be summarized as frequencies, percentages and continuous data as descriptive statistics (number of patients, mean, SD, median, minimum value, and maximum value). Demographic data will include age, gender, race, ethnicity, weight, and disease specific baseline characteristics that will be detailed in SAP.

## 11.6 Analysis Sets

The analysis sets are described below.

### 11.6.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all randomized patients who have received at least one dose of study drug with a baseline and one post baseline BCVA measurement. The FAS will be the primary population for analysis.

### 11.6.2 Per Protocol Analysis Set (PPS)

The Per Protocol Analysis Set will include all patients in the FAS without any major protocol deviation.

### 11.6.3 Safety Analysis Set (SAF)

Safety Analysis Set will include all patients who receive at least one dose of study medication. SAF will be used for all safety analyses.

### 11.6.4 Immunogenicity Analysis Set (IGS)

The immunogenicity analysis set (IGS) will include all patients who receive at least one dose of study medication and subsequently provide a valid post-baseline immunogenicity result.

## 11.7 Efficacy Analysis

### 11.7.1 Primary Efficacy Endpoint

The primary endpoint is mean change in BCVA from baseline in the study eye at the end of 12 months, assessed with the ETDRS chart.
The primary endpoint will be analyzed using ANCOVA model with fixed-effect treatment, and baseline BCVA as covariate.

Denote the population parameter for the mean change from baseline in BCVA by $\theta_R$ for LUBT010 arm, and by $\theta_L$ for Lucentis® arm, expressed in letters. The hypothesis to be tested will be

$$H_0: \ \theta_R - \theta_L \leq -4 \text{ or } 4 \leq \theta_R - \theta_L \text{ versus } H_A: \ -4 < \theta_R - \theta_L < 4.$$

The hypothesis will be tested using the two-sided 90% confidence interval for the difference as accepted by US FDA. If the 90% confidence interval lies wholly between -4 and 4, then the

null hypothesis will be rejected. The confidence interval will be constructed using a two-sample t-test.

Similar methodology will be used with 95% CI of mean difference for EMA. Thus, if 95% (2-sided) confidence interval, lies wholly within the equivalence margin (-4, 4), then the null hypothesis will be rejected.

Missing data in the primary endpoint will be imputed by multiple imputation approach under the assumption of outcome is Missing At Random (MAR). The MAR assumption will be implemented using ANCOVA model by repeated imputation of missing values in primary endpoint. For this assumption, missing outcomes are modeled using observations from a patient's own treatment arm. Thus, MAR would tend to reflect in the missing data any observed differences between treatment groups and is appropriately conservative for the objective of assessing equivalence. Then, to assess the robustness of MAR assumption in primary analysis, the sensitivity analysis via tipping point approachunder the Missing Not At Random (MNAR) assumption will be performed.
Details will be provided in the SAP, which will be finalized and signed prior to database lock and unblinding

### 11.7.2 Secondary Efficacy Endpoints

The secondary endpoints for this study are:

- Mean change in BCVA from baseline in the study eye at the end of 3 months, assessed with the ETDRS chart.
- Mean change in BCVA from baseline in the study eye at the end of 6 and 9 months, assessed with the ETDRS chart.

All efficacy endpoints will be summarized descriptively by treatment and time point. Continuous endpoints will be presented using sample size, mean, SD, minimum, median, and maximum, and categorical will be presented using sample size and percentages. Summarization will be presented for both PPS and FAS. For these summaries, no imputation of missing data will be used.

### 11.7.3 Exploratory Endpoint

The exploratory endpoint for the study is:

- Mean change from baseline in NEI-VFQ-25 Version 2000 (interviewer administered) scores at 3, 6, and 12 months.

The NEI-VFQ-25, Version 2000, will be administered by the interviewer at baseline, 3, 6, and 12 months, and the scores obtained will be summarized using number of patients, mean, SD, minimum, median, and maximum, by treatment group and scheduled visit. No imputation will be performed. Data from exploratory endpoints will be summarized using appropriate descriptive statistics and also listed as applicable. Details will be provided in SAP.

## 11.8 Safety Analysis

The safety data will be summarized and listed. Detailed statistical methodology will be described in SAP.

### 11.8.1 Parameters for Assessment of Safety

- AE assessment, ocular and non-ocular
- Ophthalmic examination
- Physical and systemic examination
- Vital signs
- ECGs
- Laboratory parameters: Blood (hematology and biochemistry) and urinalysis

#### 11.8.1.1 Adverse Events

All AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher. Events will be classified as TEAEs if they start on or after the date of the first dose of study medication. The number of AEs and the number and percentage of patients experiencing AEs will be summarized by severity and relationship to the study medication. SAEs and AEs leading to premature study discontinuation will be summarized. The corresponding listings will be provided. Study drug injection sites will be assessed for injection site reactions/ inflammatory reactions at each study visit.

#### 11.8.1.2 Ophthalmic Examination

Ophthalmic examination findings will be summarized using appropriate descriptive statistics and also listed as applicable.

#### 11.8.1.3 Physical & Systemic Examinations and Electrocardiogram Measurements

Changes in the physical and systemic examinations and 12-lead ECG findings from screening to the end of IP will be listed.

#### 11.8.1.4 Laboratory Data

Descriptive statistics will be performed for laboratory parameters at each scheduled visit and for the changes from baseline, by treatment and time point. For continuous outcomes, summaries will include sample size, mean, SD, minimum, median, and maximum. Abnormal values in each treatment arm will be determined and listed using reference ranges provided by the central laboratory. All laboratory results will be listed, including data from the unscheduled visits.

#### 11.8.1.5 Vital Signs

Changes in vital signs (pulse rate, respiratory rate, body temperature, blood pressure) from baseline to vital signs assessment at subsequent visits will be summarized. The corresponding listing will be provided.

#### 11.8.1.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO-Drug Dictionary classification and a listing will be prepared. All medications that are ongoing during the study and concomitant medications received after randomization will be summarized.

#### 11.8.1.7 Analysis of Immunogenicity

The immunogenicity data reflect the proportion of patients whose test results will be considered positive for antibodies to ranibizumab in immunoassays. The incidence of immunogenicity to ranibizumab will be tested between treatment arms on Day 1 and at the end of 1, 3, 6, 9, and 12 months.
A similar analysis will be performed for the proportion of patients with positive neutralizing antibodies to ranibizumab.
In this study, if at least one sample tests positive in the validated method during this study, the patient is evaluated as a positive patient.
Details about analysis of immunogenicity will be provided in the SAP.

#### 11.8.1.8 Extent of Exposure

Study compliance and the extent of exposure to the study medication will be summarized.

#### 11.8.1.9 Patient Discontinuation

All patients who discontinued from treatment and study will be listed and the reasons for discontinuation will be tabulated.

# 12 DATA MANAGEMENT

## 12.1 Data Handling

Data will be recorded at the site in source documents and will be transcribed in the eCRFs promptly in English and the Investigator shall verify the accuracy of data in the eCRF.

The Investigator shall maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination including ophthalmic examination reports.

Data from external sources (such as laboratory data) will be appropriately handled into the database. Medical information will be coded using MedDRA and WHO Drug Dictionary.

The monitor assigned to the site will verify the data recorded in the eCRF with source documents. The monitor confirms whether reporting is complete and that there are no contradictions by inspecting the eCRF. The monitor checks for contradictions between documents based on data in the eCRF by source data verification. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF system.

# 13 CLINICAL STUDY MANAGEMENT

## 13.1 Conduct of the Study

Lupin will conduct the study according to written standard operating procedures to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH Good Clinical Practice (GCP) E6 (R2) and applicable regulatory requirements.

## 13.2 Direct Access to Source Data

During the course of the study, the monitor will review protocol compliance, compare eCRFs and individual patient medical records, assess drug accountability records and ensure that the study is being conducted according to applicable regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

A review of the eCRFs for completeness, accuracy, legibility, timeliness, and clarity, as well as with source documents will be required to monitor the progress of the study. Moreover, the applicable regulatory authorities, Institutional Review Boards (IRBs), Institutional Ethics Committees (IECs) and/ or the Sponsor designated Clinical Quality Assurance team may perform source data checks and/ or on-site audits/ inspections to confirm the validity of the trial conduct and the integrity of data collected. Direct access to the source data will be required for these inspections and audits; these will be carried out giving due consideration to data protection and medical confidentiality. The Investigator must ensure provision of the necessary support to the Sponsor/ Sponsor's representative, regulatory or IEC/IRBs at all times.

## 13.3 Amendments to the Protocol

Important changes to the protocol and study design require a mutual agreement between the Investigator and Sponsor and will be effective following approval of the IRB/IEC and regulatory authorities (as necessary). These changes are to be described in the revised protocol and a list of changes detailing the pre-change and post-change versions will be prepared.

## 13.4 Guidance and Supervision of Sub-Investigators

The Principal Investigator shall maintain the list of appropriately qualified sub-investigators and study support staff (e.g. pharmacists, nurses and other staff) to whom significant trial-related duties have been delegated.

The Principal Investigator shall ensure that all sub-investigators and study support staff participating in the trial are adequately trained on the protocol, the IP(s) and their trial-related duties and functions and they are timely informed of any new information pertaining to the study.

## 13.5 Archiving Study Records

The essential study documents should be retained and archived until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. However, these documents should be retained for a longer period, if required by the applicable regulatory requirements or by an

agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/ institution as to when these documents no longer need to be retained.

# 14 QUALITY ASSURANCE AND QUALITY CONTROL

The Sponsor will implement and maintain quality control and quality assurance procedures to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP E6 (R2), applicable regulatory requirements, and institutional research policies and procedures.

## 14.1 Monitoring

The Investigator acknowledges that the monitor has the responsibility to review the clinical trial data for verification of proper recording and to verify the source data against the eCRF and to review the conduct of the clinical trial in compliance with the protocol and GCP. The Investigator will permit the site monitor to review study data as frequently as deemed necessary.

The Investigator may not recruit patients into the study until such time that a visit has been made by a Sponsor monitor/representative, or with the agreement of the Sponsor/ formal training by Sponsor, to conduct a detailed review of the protocol and eCRF.

The Investigator must cooperate with the Sponsor to ensure that the conduct of the clinical trial is GCP compliant.

## 14.2 Agreement and Compliance with the Protocol

Prior to trial initiation, the protocol/ other related documents must be approved by the IEC/IRB/ regulatory authority in compliance with applicable regulatory requirements. Before the first patient is allowed to participate in the clinical trial, the Sponsor must ensure that all the ethical and legal requirements are met.

The Investigator should not deviate from the protocol approved by the IRB/ IEC, except when the changes are necessary to eliminate a risk to the patients. This trial must accurately comply with the protocol. If changes to the protocol are required, the changes must be made in writing and notified or submitted for approval by the IRB/IEC/ regulatory authorities (as necessary).

## 14.3 Audits and Inspections

An auditor from the Sponsor, the regulatory authorities, or the IEC/IRBs may conduct an audit or inspect the clinical sites.
The purpose of audits and inspections is to systematically and independently verify that study-related activities are performed, data in clinical studies are accurately recorded, analyzed and reported and that the study has been conducted in accordance with protocol, ICH- GCP E6 (R2) guidelines, and the applicable regulatory requirements.
Regulatory authorities will communicate the purpose of the inspection to the Investigator and the Investigator should notify the Sponsor of the inspection. The Sponsor may provide support to the Investigator so that the site is inspection ready.

# 15 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

This study will be conducted in compliance with the protocol and with the ICH-GCP E6 (R2) guidelines for Technical Requirements for Registration of Pharmaceuticals for Human use, the World Medical Association Declaration of Helsinki (2013) and in compliance to the specific local regulatory requirements wherever applicable and required.

## 15.1 IEC/IRB Approval

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol, informed consent document and other applicable study documents have been reviewed and approved by an EC. The EC will be appropriately constituted and perform its functions in accordance with ICH- GCP E6 (R2) and local requirements as applicable.

## 15.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each patient (or their legally acceptable representative). Before each patient is enrolled into the study, informed consent will be obtained from the patient (or his/her legally acceptable representative) according to the most current applicable regulatory and legal requirements. The consent will be obtained on the IEC/IRB approved and most recent version of consent form in language best comprehended by the patient. The consent documents to be used for the study will include all the elements of informed consent as outlined in the applicable regulatory guideline and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki and be reviewed and approved by the appropriate EC prior to use at each site.

The patients should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The patients will be re-consented as required.

## 15.3 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without the prior written approval from the Sponsor. The anonymity of the participating patients must be maintained. Patients will be identified on the eCRF and other documents submitted to the Clinical Research Organization or the independent data management center by unique coded patient identification/ registration number but not by name. The confidentiality of records that could identify patients (e.g., the signed informed consent) should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s) and should only be disclosed to the authorized study personnel/ Sponsor representative/ IEC/Regulatory authorities if required.

## 15.4 Liability and Insurance

The Sponsor will obtain a reasonable third-party liability insurance coverage in accordance with all local legal regulatory requirements.

The Sponsor will provide for insurance coverage with respect to liability caused by trial-related injuries caused by IPs being tested or by study-related procedures/ medical steps taken in the course of the study in accordance with the applicable regulatory requirement(s). The terms and conditions will apply as specified in the insurance policy document.

## 15.5 Publication Policy

The Sponsor shall retain the sole and exclusive ownership of any and all data arising (whether directly or indirectly) out of the conduct of clinical trials in relation to the Study ("Data"). Upon completion of the Study, the Sponsor may, at its sole discretion, arrange the analysis and tabulation of the Data. Sponsor shall be entitled to utilize the Data and clinical study report in any manner whatsoever including using the same for publication, presentation at scientific meetings or for submission with regulatory authorities in the manner it deems fit. Investigator hereby agrees and acknowledges that it shall not use and/or publish the data and/or any reports, presentation, information arising out of or in relation to the clinical trial without prior written approval of Lupin.

Since such global studies are published with data of all patients pooled and analyzed together, isolated and independent publications at site/country level may provide inaccurate representation of safety, efficacy or immunogenicity of the investigational product. Hence, if the Investigators would like to publish/ present any paper/poster, the Investigators should provide Lupin the draft material to review for approval of any such proposed publication/presentation or other type of disclosure before it is submitted or disclosed in order to ensure against any inadvertent disclosure of confidential information or unprotected invention. For approval by Lupin, Investigator shall send such reports, presentation, information and/or data for Lupin's review and approval at least 90 (ninety) days prior. It is hereby agreed that all proposed publications based on the Study shall be subject to the Sponsor's written approval with a possibility of denial for any reason including the reasons given above. If approved with comments from Lupin, Investigator shall incorporate all such comments suggested by the Sponsor in the publication. By signing this Protocol, Investigator agrees to unequivocally release the Data from the Study to the Sponsor without conditions and acknowledges this publication policy.

# 16 APPENDICES

## 16.1 Appendix A: Preparation for Administration

Details pertaining to preparation for administration of Investigational product is provided in Appendix A.

## 16.2 Appendix B: Study Management Details

Study management/ study administrative details is provided in Appendix B.

## 16.3 Appendix C: Investigator's Signature Page

## 16.4 Appendix D: Visual Functioning Questionnaire

The NEI-VFQ-25 to be administered by interviewer at baseline, 3, 6, and 12 months is provided in Appendix D.

## 17 REFERENCE LIST

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# Appendix: A
# Preparation for Administration

**Version: 2.2; Dated 19 May 2022**

A Global, Phase III, Double Blind, Randomized Controlled Study to Compare the Efficacy, Safety & Immunogenicity of LUBT010 with Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

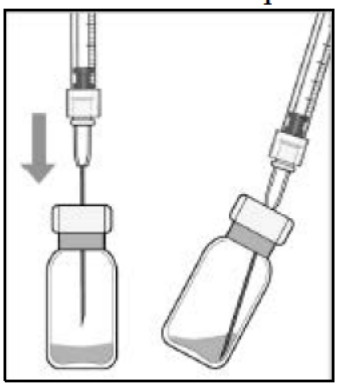
**Lupin Limited (Biotech Division)**

| | |
|---|---|
| Protocol No : | LRP/LUBT010/2016/008 |
| Version : | 2.2 |
| Date : | 19 May 2022 |
| Study drug: | Ranibizumab (LUBT010) |
| Development Phase: | Phase III |

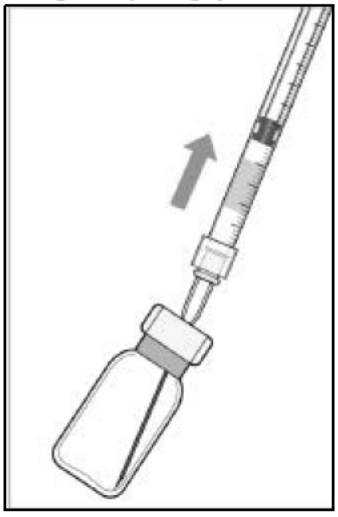
Using aseptic technique, all of the vial contents should be withdrawn through a sterile filter needle attached to a 1 mL syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile needle for intravitreal injection.

Use aseptic technique to carry out the following preparation steps:

1. Prepare for intravitreal injection with the following medical devices for single use:
   - a sterile filter needle
   - a 1 mL sterile Luer lock syringe (with marking to measure 0.05 mL)
   - a sterile injection needle
2. Before withdrawal, disinfect the outer part of the rubber stopper of the vial.
3. Place a filter needle onto a 1 mL Luer lock syringe using aseptic technique.
4. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
5. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.

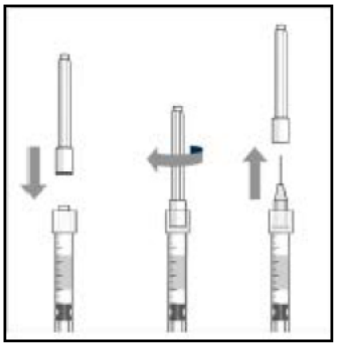


6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

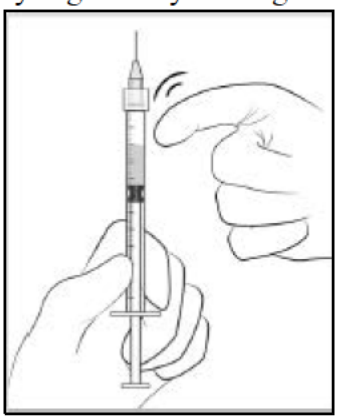


7. The filter needle should be discarded after withdrawal of the vial contents and must not be used for the intravitreal injection.

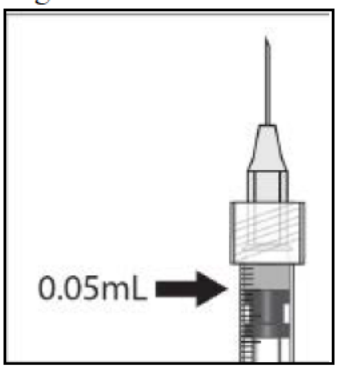
8. Attach a sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer lock. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.



9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



10. Hold the syringe at eye level, and carefully push the plunger rod until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.



# Appendix: B
# Study Management Details
**Version: 2.2; Dated 19 May 2022**

A Global, Phase III, Double Blind, Randomized Controlled Study to Compare the Efficacy, Safety & Immunogenicity of LUBT010 with Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

**Lupin Limited (Biotech Division)**

| | |
|---|---|
| Protocol No : | LRP/LUBT010/2016/008 |
| Version : | 2.2 |
| Date : | 19 May 2022 |
| Study drug: | Ranibizumab (LUBT010) |
| Development Phase: | Phase III |

## Study Management Details
## General Information

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

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

# Appendix: C
# Investigator's Signature Page Version: 2.2; Dated 19 May 2022

# INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE: A Global, Phase III, Double Blind, Randomized Controlled Study to Compare the Efficacy, Safety & Immunogenicity of LUBT010 with Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

PROTOCOL NUMBER: LRP/LUBT010/2016/008

VERSION/DATE: Version 2.2; Dated 19 May 2022

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated, or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients. I agree to conduct this study in full accordance with the protocol, all applicable regulations and Good Clinical Practice (GCP) guidelines.

Principal Investigator Name and Job Title: _____

_____

Institution/Clinic: _____

Address: _____

_____

Signature: _____

Date (day/month/year)

# Appendix: D
# Visual Functioning Questionnire

**Version: 2.2; Dated 19 May 2022**

A Global, Phase III, Double Blind, Randomized Controlled Study to Compare the Efficacy, Safety & Immunogenicity of LUBT010 with Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

**Lupin Limited (Biotech Division)**

| | |
|---|---|
| Protocol No : | LRP/LUBT010/2016/008 |
| Version : | 2.2 |
| Date : | 19 May 2022 |
| Study drug: | Ranibizumab (LUBT010) |
| Development Phase: | Phase III |

PB/IA

# National Eye Institute
# Visual Functioning Questionnaire - 25
# (VFQ-25)

version 2000

# (INTERVIEWER ADMINISTERED FORMAT)

January 2000

## Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

# Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

**1. In general, would you say your overall health is*:**

*(Circle One)*

**READ CATEGORIES:**

**Excellent ..... 1**
**Very Good ..... 2**
**Good ..... 3**
**Fair ..... 4**
**Poor ..... 5**

**2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?**

*(Circle One)*

**READ CATEGORIES:**

**Excellent ..... 1**
**Good ..... 2**
**Fair ..... 3**
**Poor ..... 4**
**Very Poor ..... 5**
**Completely Blind ..... 6**

---

*** Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

**3. How much of the time do you worry about your eyesight?**

*(Circle One)*

**READ CATEGORIES:**

| | |
|---|---|
| **None of the time** | **1** |
| **A little of the time** | **2** |
| **Some of the time** | **3** |
| **Most of the time** | **4** |
| **All of the time?** | **5** |

**4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:**

*(Circle One)*

**READ CATEGORIES:**

| | |
|---|---|
| **None** | **1** |
| **Mild** | **2** |
| **Moderate** | **3** |
| **Severe, or** | **4** |
| **Very severe?** | **5** |

PART 2 - DIFFICULTY WITH ACTIVITIES

**The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.**

**5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**6. How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**7. Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**8. How much difficulty do you have <u>reading street signs or the names of stores</u>?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**9. Because of your eyesight, how much difficulty do you have <u>going down steps, stairs, or curbs in dim light or at night</u>?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**10. Because of your eyesight, how much difficulty do you have <u>noticing objects off to the side while you are walking along</u>?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**11. Because of your eyesight, how much difficulty do you have <u>seeing how people react to things</u> you say?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**12. Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**13. Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u>?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**14. Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Stopped doing this because of your eyesight** | **5** |
| **Stopped doing this for other reasons or not interested in doing this** | **6** |

**15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?**

*(Circle One)*

**Yes ..... 1** *Skip To Q 15c*

**No ..... 2**

**15a. IF NO, ASK: Have you never driven a car or have you given up driving?**

*(Circle One)*

**Never drove ..... 1** *Skip To Part 3, Q 17*

**Gave up ..... 2**

**15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?**

*(Circle One)*

**Mainly eyesight ..... 1** *Skip To Part 3, Q 17*

**Mainly other reasons ..... 2** *Skip To Part 3, Q 17*

**Both eyesight and other reasons .... 3** *Skip To Part 3, Q 17*

**15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:**

*(Circle One)*

**No difficulty at all ..... 1**
**A little difficulty ..... 2**
**Moderate difficulty ..... 3**
**Extreme difficulty ..... 4**

**16. How much difficulty do you have <u>driving at night</u>? Would you say you have:** (READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Have you stopped doing this because of your eyesight** | **5** |
| **Have you stopped doing this for other reasons or are you not interested in doing this** | **6** |

**16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:**
(READ CATEGORIES AS NEEDED)

*(Circle One)*

| | |
|---|---|
| **No difficulty at all** | **1** |
| **A little difficulty** | **2** |
| **Moderate difficulty** | **3** |
| **Extreme difficulty** | **4** |
| **Have you stopped doing this because of your eyesight** | **5** |
| **Have you stopped doing this for other reasons or are you not interested in doing this** | **6** |

PART 3: RESPONSES TO VISION PROBLEMS

**The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you <u>all</u>, <u>most</u>, <u>some</u>, <u>a little</u>, or <u>none</u> of the time.**

| **READ CATEGORIES:** | *(Circle One On Each Line)* **All of the time** | **Most of the time** | **Some of the time** | **A little of the time** | **None of the time** |
|---|---|---|---|---|---|
| **17. <u>Do you accomplish less</u> than you would like because of your vision?.....** | **1** | **2** | **3** | **4** | **5** |
| **18. <u>Are you limited</u> in how long you can work or do other activities because of your vision?.....** | **1** | **2** | **3** | **4** | **5** |
| **19. How much does pain or discomfort <u>in or around your eyes</u>, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:.....** | **1** | **2** | **3** | **4** | **5** |

**For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.**

*(Circle One On Each Line)*

| | Definitely True | Mostly True | Not Sure | Mostly False | Definitely False |
|---|---|---|---|---|---|
| **20. I stay home most of the time because of my eyesight.....** | **1** | **2** | **3** | **4** | **5** |
| **21. I feel frustrated a lot of the time because of my eyesight.....** | **1** | **2** | **3** | **4** | **5** |
| **22. I have much less control over what I do, because of my eyesight.....** | **1** | **2** | **3** | **4** | **5** |
| **23. Because of my eyesight, I have to rely too much on what other people tell me....** | **1** | **2** | **3** | **4** | **5** |
| **24. I need a lot of help from others because of my eyesight.....** | **1** | **2** | **3** | **4** | **5** |
| **25. I worry about doing things that will embarrass myself or others, because of my eyesight.....** | **1** | **2** | **3** | **4** | **5** |

**That's the end of the interview. Thank you very much for your time and your help.**