21 May 2026
EMA/CHMP/116885/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vislyfa

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/006926/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

AE	Adverse Event
ADA	Anti-drug antibodies
ADR	Adverse Drug Reaction
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis Of Covariance
AR	Assessment Report
ATC	Anatomical Therapeutic Chemical (class)
BCVA	Best Corrected Visual Acuity
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNV	Choroidal Neovascularization
Cmax	Peak serum concentration
CRF	Case Report Form
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CSR	Clinical Study Report
Ctrough	The concentration reached by a drug immediately before the next dose is administered
DME	Diabetic Macular Oedema
DP	Drug Product
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFC	Enzyme Fragment Complementation
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
ENR	Enrolled Set
EOS	End Of Study
EOT	End Of Treatment
ERA	Environmental Risk Assessment
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography/Fundus Fluorescein Angiography
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICE	Intercurrent Events
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGS	Immunogenicity Analysis Set
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IRB	Institutional Review Board
IVT	Intravitreal
IWRS	Interactive Web Response System
LS Mean	Least Squares Mean
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAR	Missing At Random
MedDRA	Medical Dictionary For Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model For Repeated Measures
MNAR	Missing Not At Random
MSD-ECL	Meso Scale Discovery using Electrochemiluminescence
NAbs	Neutralizing Antibodies
nAMD	Neovascular Age-Related Macular Degeneration
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25-Item
NOAEL	No Observed Adverse Effect Level
OCT	Optical Coherence Tomography
PD	Pharmacodynamic(s)

PD	Protocol Deviation
PDT	Photodynamic Therapy
PFS	Pre-Filled Syringe
PI	Principal investigator
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PPS	Per Protocol Analysis Set
PRAC	Pharmacovigilance Risk Assessment Committee
PDR	Proliferative Diabetic Retinopathy
PT	Preferred Term
QA	Quality Assurance
QOL	Quality Of Life
QTL	Quality Tolerance Limit
RAN	Randomised Set
RDTS	Repeat-Dose Toxicity Study
RMP	Risk Management Plan
RefMP	Reference Medicinal Product
RVO	Retinal Vein Occlusion
SA	Scientific Advice
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of product characteristics
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TMF	Trial Master File
US-FDA	United States Food And Drug Administration
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor

1. Regulatory information and recommendations on the procedure

1.1. Information on the product

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality/ non-clinical/ clinical)*	*Reference number / Coordinator(s)*	*Brief summary of the advice*
23 June 2016	Quality, non-clinical, clinical	EMEA/H/SA/3346/1/2016/III Dieter Deforce and Jan Mueller-Berghaus.	• Sourcing of the reference medicinal product for the physicochemical and functional comparability exercise; appropriateness of the physicochemical methods for the comparability exercise; number of batches in the panel of physicochemical and *in vitro* assays; the methods used in the planned *in vitro* studies to demonstrate binding and biological activity. • Adequacy of the pre-clinical development programme. • The proposal to omit a pharmacokinetics (PK)/pharmacodynamics (PD) study of intravitreally (IVT) injected ranibizumab; the design of a comparative study ranibizumab biosimilar candidate 0.5 mg and Lucentis 0.5 mg in patients with neovascular age-related-macular degeneration to assess efficacy, safety, and immunogenicity including endpoints, choice of primary efficacy analysis population, equivalence margin, duration of immunogenicity testing, source country of the comparator, patient ethnicity; extrapolation of clinical data to the other approved indications of ranibizumab.

1.3. Eligibility to the centralised procedure

The applicant Lupin Europe GmbH submitted on 2 March 2026 an application for marketing authorisation to the European Medicines Agency (EMA) for Vislyfa (Ranibizumab), through the centralised procedure. This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a multiple of Ranluspec authorised on 10 February 2026. The eligibility was granted by the CHMP on 11 December 2025.

The applicant applied for the following indication:

Vislyfa is indicated in adults for:

– The treatment of neovascular (wet) age-related macular degeneration (AMD)

- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

1.4. Legal basis and dossier content and multiples

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

This application is submitted as a multiple of Ranluspec authorised on 10 February 2026 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with European Union provisions in force for not less than 8 years in the EEA.

Product name, strength, pharmaceutical form:	Lucentis 10mg/ml solution for injection
Marketing authorisation holder:	Novartis Europharm Limited
Date of authorisation:	22/01/2007
Marketing authorisation granted by:	European Union
Marketing authorisation number:	000715

1.5. Information on paediatrics

Not applicable.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Daniela Philadelphy
Co-Rapporteur:	Simona Badoi

The application was received by the EMA on	02 March 2026
The procedure started on	23 March 2026
The CHMP and PRAC Rapporteurs first Joint Assessment Report was received on	28 April 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 May 2026
The CHMP Rapporteur circulated the CHMP and PRAC updated Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	11 May 2026
The Biologics Working Party agreed on the Assessment Overview during their meeting on	13 May 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vislyfa on	21 May 2026

1.8. CHMP outcome

1.8.1. Considerations related to paediatrics

Not applicable.

1.8.2. Considerations related to orphan market exclusivity

Not applicable.

1.8.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vislyfa is favourable in the following indication(s):

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.8.4. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Vislyfa is considered biosimilar to Lucentis. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

1.8.5. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.8.6. Other conditions and requirements of the marketing authorisation

1.8.6.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.7.1. Risk management plan (RMP)

The Marketing Authorisation Holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.8.7.2. Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that, following discussions and agreements with National Competent Authorities (NCA) in each member state where Vislyfa is marketed, at launch and after launch, all ophthalmological clinics where Vislyfa is expected to be used for treatment of adult patients are provided with an up-to-date patient information booklet (including audio format).

Key messages of the additional risk minimization measures for adult patients in the indications of nAMD, CNV, DME, RVO and PDR

The patient booklet

The patient educational material will be developed and will be made available as per communication plan agreed with NCA in each member state, in order to support the safe use of ranibizumab. The patient booklet provides information on the key signs and symptoms of potential adverse reactions, ensuring rapid identification and treatment of these events.

The patient information pack should be provided in both the form of patient booklet and in audio format that will contain following key elements:

- Patient information leaflet
- How to prepare for Vislyfa treatment
- What are the steps following treatment with Vislyfa
- Key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis
- When to seek urgent attention from the health care provider

Details of proposed educational program for adult patients

To ensure that patients are adequately informed about potential adverse events of ranibizumab, a patient information booklet will be made available.

The booklets aim to provide adequate patient education on:

- What is nAMD, CNV (including secondary to pathologic myopia), PDR with or without DME, and RVO
- How does ranibizumab work, what to expect from ranibizumab treatment, and how is ranibizumab administered
- What are the key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis
- When to seek urgent attention from the health care provider

Key safety messages are focused on facilitating the patient recognizing the key signs and symptoms of potential adverse reactions to ensure the patient informs their ophthalmologist of these potentially severe outcomes. The following are the key safety messages to be communicated to allow early diagnosis and appropriate treatment of these events:

- It is important that patients monitor any changes in the condition of their eye and their overall wellbeing in the week following injection with ranibizumab.
- Patients need to contact their clinic immediately if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light.

In addition, the booklet contains follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.

1.8.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.8.9. Proposed list of recommendations

Table 2: Proposed list of recommendations

Description of Recommendation(s)
The applicant committed to further evaluate approaches to decrease the variability observed for polysorbate 20 method.

2. Introduction

2.1. Therapeutic Context

A similar biological application was submitted for Vislyfa (ranibizumab) according to Directive 2001/83, Article 10(4). The administration route (IVT injection), presentation (solution for injection in vial and pre-filled syringe [PFS], 10 mg/mL), posology and indications were proposed according to the EU-approved reference medicinal product (RefMP) Lucentis, except for the treatment of retinopathy of prematurity (ROP) in preterm infants, which had been granted marketing authorisation (MA) in the EU on 22 January 2007.

2.2. Aspects of development

Clinical

The aim of the clinical development was to demonstrate biosimilarity between Vislyfa and the reference product in terms of clinical pharmacology, efficacy and safety, not to establish patient benefit per se. A positive benefit/risk balance had already been established for the reference product Lucentis.

For this purpose, two clinical studies were conducted as follows:

- Study LRP/LUBT010/2022/001: PK, PD, safety and immunogenicity were compared in order to demonstrate similarity between Vislyfa and Lucentis in neovascular age-related macular degeneration (nAMD) patients.
- Study LRP/LUBT010/2016/008: A clinical Phase 3 study in patients with nAMD was conducted to demonstrate similarity in efficacy immunogenicity and safety profiles between Vislyfa and Lucentis.

2.3. Description of the product

Vislyfa has been developed as biosimilar medicinal product to the reference product Lucentis (Ranibizumab) and is a duplicate application to Ranluspec (EMEA/H/C/006502).

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and choroidal neovascularization (CNV) or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to retinal vein occlusion (RVO) in adults.

Vislyfa is indicated in adults for:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No pre-approval inspection was required by the CHMP.

For the AS manufacturing site Lupin Limited (Biotech Division), Gat No. 1156, 1157, 1158, 1159 & 1160 Village Taluka Mulshi, Ghotawade, Pune, Maharashtra, India – 412 115, a valid EU GMP certificate is available through the EudraGDMP database, however it has been restricted only for the production of a different substance. Based on the outcome of the last GMP inspection at the Lupin site in September 2024 (no major deficiencies), and the fact that many of the pharmaceutical quality system GMP principles employed are similar, it is considered that the inspection for manufacture and quality control of the Ranibizumab active substance can be deferred to the next planned inspection, to allow the product assessment to progress.

For the FP manufacturing site, a valid GMP certificate is available in EudraGMP database. However, certificate seems to be restricted to medicinal products that were subject to GMP inspection, and it does not include Ranibizumab finished product. Based on the outcome of the last GMP inspection at the Lupin site in June 2024 (no major deficiencies), and the fact that many of the pharmaceutical quality system GMP principles employed for manufacture of finished product are similar and that the equipment used for finished product filling is the same that has been in scope of that last inspection, it is considered that the inspection for manufacture and quality control of the Ranibizumab finished product can be deferred to allow the product assessment to progress.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection was required by the CHMP.

2.4.3. Good clinical practice (GCP) inspection(s)

A request for a routine GCP inspection was adopted for the pivotal clinical study LRP/LUBT010/2016/008 and concerned two study sites as well as the Sponsor. The integrated inspection report noted 1 critical finding at site in Country 1 as well as 4, 9 and 6 major findings at site in Country 2, site in Country 1and the sponsor, respectively. The critical finding concerned manipulation of essential metadata of intraocular pressure (IOP) measurements and a general lack of understanding for essential GCP principles. Thus, the clinical study conduct at site in Country 1was considered not compliant with ICH GCP and reported data not trustworthy). The inspection team considered this a site-specific issue and an isolated case. The inspectors recommended to exclude the data from the Country 1site from the trial data assessment in support of the Marketing Authorisation Application (MAA).

Besides the mentioned site-specific critical finding, other major findings at the inspected sites and the sponsor pertained to inadequate TMF management, shortcomings in the documentation of the IMP and clinical sample management at the study sites and clinical data management at the sponsor, delayed reporting of one SAE at site in Country 1, and the fitness of the blinding solution. In addition, discrepancies between source data and data that was transcribed into the eCRF were reported, but in contrast to site in Country 1, without an identified "substantial impact on endpoint data" concerning site in Country 2. Another major finding pertained to shortcomings at the central reading unit, leading the randomisation of two ineligible patients. Concerning the sponsor's quality assurance system, a major finding was raised as the vendor management was deemed inadequate as the CRO employed for

the global conduct of the study as well as subcontracted vendors were not considered for auditing based on risk. In accordance with the Integrated Inspection Report "the trial data reported for clinical trial LRP/LUBT010/2016/008 is considered to be of sufficient integrity and quality to be used in the evaluation process of the MAA by the assessors, despite observed deficiencies at the investigator site in Country 2and the sponsor site." (except for trial data reported from the Country 1site).

3. Quality aspects

3.1. Introduction

Vislyfa has been developed as biosimilar medicinal product to the reference product Lucentis and is a duplicate application to Ranluspec.

Ranibizumab (INN) is a recombinant humanized IgG1 kappa isotype Fab fragment of a recombinant humanized antibody (rhuMAb) VEGF produced in Escherichia coli cells by recombinant DNA technology. It is an antagonist of human VEGF-A.

The finished product (FP) is presented as solution injection containing 10 mg/mL of ranibizumab as active substance (AS).

Other ingredients are: α,α-trehalose dihydrate, histidine hydrochloride, monohydrate histidine, polysorbate 20 and water for injections.

The product is available in a single-use Type I glass vial with a stopper (chlorobutyl rubber) (2.3 mg/0.23 ml) or in a single-use PFS (Cyclo olefin polymer) (1.65 mg/0.165 ml) with a chlorobutyl rubber plunger stopper with i-coating (silicone resin coating) and a syringe cap consisting of a translucent, tamper-evident rigid seal with a chlorobutyl rubber tip cap including a Luer lock adapter. The PFS has a plunger rod and a finger grip and is packed in a sealed tray.

3.2. Active substance

3.2.1. General information

Ranibizumab (LUBT010) is the Fab moiety of a recombinant humanised Immunoglobulin G1 monoclonal antibody, with approximately 48 kDa. It contains 10 cysteine residues forming 4 intra-chain and 1 inter-chain disulfide bonds. Being a Fab fragment, ranibizumab does not contain the Fc region that is involved in antibody-mediated effector functions, and the protein is not glycosylated as it is produced in E. coli. The name LUBT010 is used for both the active substance and finished product in this application.

General information of ranibizumab has been provided in sufficient detail.

3.2.2. Manufacture, characterisation, and process controls

The active substance is manufactured at Lupin Limited (Biotech Division), Maharashtra, India. Valid proof of GMP compliance has been provided for all sites involved in manufacturing, testing and release of ranibizumab AS.

Description of the manufacturing process and process controls

The upstream process starts with the thawing of a single vial of the Working cell bank (WCB), followed by inoculation and incubation under predefined conditions for expansion of the culture until the growth criteria are met. At the end of fermentation process, cells are separated from fermentation broth by centrifugation, and the resultant cell mass is resuspended and lysed. The IBs are isolated and stored until further processing.

The IBs are thawed before initiating the downstream process. After refolding, the refolded protein is then concentrated and diafiltered. The concentrated protein is purified via multiple chromatographic steps to capture the protein of interest and to remove process/product related impurities, followed by buffer exchange to achieve protein concentration equivalent to AS concentration. The AS is filled and stored at recommended storage conditions.

Details of the media, reagents, buffers, column cleaning and storage solutions used in each stage of upstream and downstream process are provided. The chromatography resins and filters are listed, and representative chromatograms are included for each chromatography step. Hold times for media, buffers, and in-process materials are summarized.

Batch numbering system, batch scale, and batch size are adequately presented. A detailed flow-chart of AS manufacturing process is provided and includes process inputs/parameters and in–process controls/testing.

The approach for the classification of process parameters (critical process parameters (CPP), non-CPP) and definition of operating ranges (Manufacturing Operating Range (MOR), Normal Operating Range (NOR) and Proven Acceptable Range (PAR)) follows recommendations of the ICH Q8(R2) guideline. CPPs and non-CPPs, along with their respective PARs, have been established for each unit operation in process characterization studies. NOR and MOR are the embedded ranges within the PAR and are established to ensure tighter control during routine operations. The testing approach has been adapted for process parameter controls which includes in-process control (IPC) and in-process testing (IPT). Acceptance criteria are pre-defined for IPCs, while action limits are defined for IPTs. The actions to be triggered in case of excursions from operating ranges and process controls criteria/limits are sufficiently explained. Proposed PPs/IPCs are well presented, in tabular form for each step, with their classification and operation ranges set.

Reprocessing can be performed in defined situations.

Control of materials

Compendial and non-compendial raw materials used in upstream and downstream processing are listed, with representative Certificates of Analysis attached. Specifications and descriptions of analytical methods are provided for non-compendial materials, while references to Ph. Eur. are given for compendial materials, which is acceptable. Chromatography resins, UF/DF membranes, and filters, along with test parameters and acceptance criteria, are also listed. The provided data are acceptable.

The cell substrate for the production of ranibizumab consists of E. coli host cell expression system. The clone/cell line development is described in sufficient detail, including the data on cloning and expression hosts and vectors (source, gene construction, nucleotide sequence, host genotype, vector map, the cloning procedure, vector construct characterization), in line with principles and recommendations given in ICH Q5B.

Expression analysis, SDS-PAGE and RP-HPLC confirmed the presence of heavy and light chains (HC and LC) as insoluble fractions within the E. coli cells. Analysis of nucleotide sequence of pet HC-LC construct (Research cell bank (RCB) characterization) confirmed that cloned HC and LC sequence is identical to theoretical ranibizumab sequence included in the reference product Lucentis.

Preparation, general information and storage conditions of RCB, master and working cell banks (MCB, WCB) and End of Production Cell Bank (EPCB) is sufficiently described. Cell banks were characterised in accordance with the requirements of ICH Q5D. A protocol for the establishment and control of future WCBs is provided.

The active substance manufacturing process has been adequately described.

Control of critical steps and intermediates

The CPPs and non-CPPs with defined ranges (PAR, MOR, NOR), identified for individual unit operations in the manufacturing process, are tabulated. The justification presented for PP classification and proposed ranges, based on the outcome of Process Characterisation studies and process/scientific knowledge, as well as the overall manufacturing control strategy, is deemed acceptable.

In-process bioburden and endotoxin action limits, used to demonstrate microbial controls of the manufacturing process, are presented and considered appropriate. Culture purity is proposed as an IPC at the seed and fermenter stage, which is acknowledged.

For details on the IPC analytical methods and their validation, the applicant refers to CTD sections S.4.2 and S.4.3, except for culture purity, for which sufficient data (method description, qualification) is provided.

Inclusion bodies (IBs) are defined as a critical intermediate in the AS manufacturing process. The proposed specification includes RP-HPLC purity testing (Main form, LC and HC content). The presented hold time/stability data demonstrate that the IBs can be stored at the recommended storage condition before being used in future processing.

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation and/or evaluation

Validation of manufacturing process is appropriately designed, in line with relevant guidelines and includes sufficient number of commercial scale batches. Consecutive commercial scale AS batches were obtained from consecutive upstream batches (from WBC vials) in such way that upstream batches of IBs were pooled and further processed through downstream processing steps to manufacture each AS batch.

In accordance with the description of the manufacturing process, the validation exercise was performed across all process steps. A specific panel of tests, including routine in-process control tests, process parameters (CPP, non-CPP) and additional tests (IPM), was identified and monitored to provide detailed information on the consistency of the manufacturing process. The results of CPPs/non-CPPs were within the respective NOR range, demonstrating that all tested parameters met the requirements. Observed excursions in dissolved oxygen profile (CPP) outside the NOR at fermentation stage were adequately justified and shown to be within the allowable time limit. The in-process results were observed to be within their acceptance criteria/ action limits, and their values were also comparable between the PPQ batches. The results of AS batch analyses and the validation data demonstrate that all unit operations of AS manufacturing process are consistent in producing a product of desired quality and meeting all established specifications.

The results of resin/membrane re-use studies using a qualified scale-down model is provided for the downstream steps. All tested parameters met pre-established acceptance criteria during the tested

cycles and based on the provided results, the resin/membrane lifetime for commercial production is specified. The reuse study conducted at small scale is being verified at manufacturing scale.

Reprocessing can be performed at the AS filtration (re-filtration) or UF/DF2 (re-concentration) step in case of a mechanical failure of the equipment, which can be considered as exceptional circumstances. A reprocessing study was performed at small scale, and the results show no significant changes in the tested parameters before and after reprocessing. Reprocessing protocol at commercial scale is deemed acceptable.

Provided hold time results for upstream and downstream buffers confirm the proposed hold times. Holding times of upstream culture media were determined in small-scale models, and the results confirmed the proposed storage conditions. The hold time study for upstream process intermediates was performed using manufacturing batches. Results met the IBs release acceptance criteria, which is acknowledged. The study for downstream intermediates was also conducted with at scale batches, and the provided results of the tested critical Quality attributes (CQAs) support the proposed hold times.

As part of Continued process verification (CPV) protocol, sampling and testing will be monitored at scale batches in the initial CPV phase followed by the data acquisition and trend analysis. The acquired data will allow to establish the statistically derived process ranges. CPV protocol will be managed within the Lupin's Quality System. Any change in the manufacturing process description and controls resulting from continued process verification will be notified to the agency under the appropriate variation category. Sufficient data are provided.

The active substance manufacturing process has been validated adequately. Consistency in production has been shown on three full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces an active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Manufacturing process changes / process versions

The applicant summarized four process versions designated as 1, 2A, 2B, and 3 (corresponding to the lab scale, pilot, and process validation (PV)/commercial process). There is no difference between the validation and the proposed commercial process, and the PPQ and post-PPQ batches were manufactured with the same process (Process 3). The rationale of implemented changes between the processes is adequately presented. A risk assessment has been performed for each change introduced from Process 2B to process validation Process 3, including classification of criticality and potential impact to AS quality attributes (QAs), in accordance with ICH Q9 (risk ranking, risk/severity score, risk management).

The list of AS batches manufactured throughout the development up to the commercial process (pre-clinical, developmental, clinical, stability, specification setting, PV, post-PV) is presented, clearly linking the batches, their intended use, and the manufacturing process versions. The batches presented are harmonised between the relevant sections of the dossier. Initial lab-scale batches were executed to optimize the protein refolding and chromatographic purification steps. This phase focused on establishing process consistency and generating material for stability and preclinical toxicity studies. After establishing the consistency at the 10 L scale fermentation, the process was linearly scaled up for the manufacturing of clinical material. Further improvements in the clinical process involved removing of ampicillin from the MCB medium to employ an antibiotics-free working cell bank (WCB) for the proposed commercial process prior to process validation. In addition, several modifications to the refolding step, filtration, and chromatographic steps were introduced to the clinical and PV process.

Comparability exercise

The comparability exercise was conducted between the developmental AS batches (preclinical, clinical) and batches intended for commercial manufacturing, with emphasis on the comparability between the material from Process 2B (clinical) and Process 3 (commercial material). The comparability panel included (i) comparison of historical/release and in-process data of clinical and PV material, (ii) side-by-side physicochemical and biological characterization of relevant QAs, and (iii) comparison under accelerated and stress conditions, in line with the ICH Q5E guideline.

The release results for each process version are presented for each tested QA. The values of the AS QAs across all three processes consistently remain within their specified limits, as well as within the mean ±3SD range established by the process 2B batches. This indicates that the quality attributes of AS are stable and supports the conclusion that there is quality comparability between all the processes. Observed minor differences in IE-HPLC and RP HPLC profiles are adequately addressed. The results for in-process testing of quality attributes were also within the proposed comparability criteria.

The extensive physicochemical and biological characterization panel included a sufficient number of relevant quality attributes, and results are presented for both clinical and commercial batches. The presented results support comparability between the clinical and commercial process in terms of structure, relative potency, binding kinetics, size variants, post translational modifications, and iso-electric point.

The comparative stability results included stability data under real-time, accelerated, and stress conditions. Based on the presented statistical evaluation there are no significant differences in the stability between the processes.

In summary, the comparability data for AS quality, assessed using release test methods, extended characterization, in-process testing, and stability data, confirm that the proposed commercial process (Process 3) is highly comparable to Process 2B, which produced the clinical material.

Analytical methods during development

A summary of changes in the analytical methods during AS development for testing preclinical, clinical and PV batches is presented. Changes to CE-SDS nr, RP-HPLC, HCP and polysorbate 20 analytical methods were introduced after the pivotal Clinical trial (CT). Changes in SE-HPLC, IE-HPLC, HUVEC, BET, and bioburden methods were introduced before the CT, and they are adequately described and justified in the dossier. Updated dossier includes a comprehensive summary of all method changes, bridging studies along with data, and justification of their suitability for setting specifications. The provided data are acceptable.

Analytical methods used during development are listed. For some methods, descriptions with qualification summaries are provided, confirming the suitability for the intended analytical purpose.

Process characterization

The process characterization studies were based on historical development, scientific understanding and a risk-based approach. All process parameters for each unit operation were subjected to Failure Mode and Effects Analysis (FMEA) risk assessment, and based on the outcome of the FMEA, process parameters were evaluated in the process characterization studies for their impact on process attributes or QAs.

Multivariate design of experiments (DOE) studies, univariate studies (One factor at a time, OFAT), and linkage studies were conducted. As an outcome of process characterization, parameters were classified into CPPs non-CPPs, along with their respective operational ranges (PAR), based on their severity of impact on product quality, performance, and interaction with other parameters.

The presented approach and the provided results of the comprehensive process characterisation studies are overall acceptable and in line with ICH Q8-Q11 guidelines.

Small-scale models for the different process steps are sufficiently described and justified. The presented models were appropriately qualified through qualification studies, demonstrating equivalence between the model and the large-scale process for selected quality attributes.

Control strategy

The process controls strategy is based on a comprehensive assessment that identifies CQAs and classifies PPs based on their impact on CQAs. The process characterization studies conducted during development phase provided an in-depth understanding of the process and ensured performance and product quality at each phase of the manufacturing. A strategy has been developed that includes manufacturing process parameters and attributes related to upstream and downstream processing, facility and equipment operating conditions, in-process testing of starting materials and process intermediates, final AS or FP specifications, as well as the associated methods and frequency of monitoring and control. An appropriate process control strategy has been implemented to ensure that the proposed commercial manufacturing consistently deliver an active substance to meet its predefined quality attributes. The risk ranking of quality attributes, along with justification for criticality scores, is performed at the FP level and for the purpose of the biosimilarity study.

Extractables and leachables studies

The risk assessment report performed to evaluate the risks of extractables and leachables from components of the materials and equipment used in the AS manufacturing process has been provided. All product-contact materials are listed (equipment, containers, filters/membranes, connectors, gaskets, tubes, etc.), along with the maximum hold duration of material at each stage. Based on the propensity ranking, only low and medium risk levels were observed for the materials. None of the materials were classified as high risk. No formal extractables and leachables studies have been performed. However, based on the provided justification, the conclusion that the product-contact components detailed in this assessment do not have an impact on the safety, identity, strength, quality, or purity of the AS, is supported.

Characterization

Elucidation of structure and other characteristics

Analytical characterization was performed using AS batches (PV process batch, PPQ batch, post PPQ batch) which were compared to primary reference standard. The primary reference standard was manufactured using AS batches representative of commercial manufacturing process.

Only some characterisation data are presented in this section. However, this is acceptable since a far more comprehensive data set is presented as part of the analytical similarity assessment.

The AS has been characterised with respect to molecular identity, primary, secondary, tertiary and higher order structure, protein content, post-translational modifications (oxidation and deamidation) and binding properties and bioactivity.

Molecular identity: Confirmation of the molecular identity was performed by peptide mapping comparing to IPRS.

Primary structure: The primary structure was characterized by various techniques including intact and reduced mass analysis. The obtained MS/MS data were compared with the theoretical masses and theoretical sequence to confirm whether the amino acid sequence of LUBT010 was consistent with the theoretical values. All tests showed the consistency between the batches and the IPRS.

For determination of protein content all AS batches had results within AS specification. The method uses extinction coefficient of 1.8.

Higher-order structure: Confirmed using orthogonal analytical techniques (secondary structure, tertiary structure, and disulphide linkage). The estimated disulfide bonds (5) and respective molecular weights of disulphide variants were comparable between batches. The overlay of the spectra show similarity between LUBT010 batches.

Post-translational modifications: Oxidation and deamidation were determined after trypsin digestion. Presented results are similar between batches even though some slight differences can be seen. These was assessed further in the biosimilarity study, as well as non-canonical amino acids norleucine (Nle) and norvaline (Nva), which are known to be mis-incorporated by microbial expression systems.

Biological characterisation: The biological activity and binding activity of LUBT010 to VEGF-A165 were determined and similar results are presented.

For all methods employed during characterisation studies brief method descriptions is provided. Overall, the selected assays are considered adequate to demonstrate the functional properties (mechanism of action) of ranibizumab, taking into account that the same batches were also used in biosimilarity exercise.

Impurities

Product-related impurities have been detailed. Identified product-related impurities include HMWS, LMW, pre and post-peaks and charge variants. Some of these have been characterised and presented. Adequate controls are in place for high molecular weight species (HMWS), low molecular weight species (LMWS), pre and post peak impurities and charge variants since they are included in the AS and FP specification. Overall, it can be concluded that product-related impurities are well controlled and are not expected to impact safety or product efficacy at the level controlled by the manufacturing process and AS specification.

The AS manufacturing process has been assessed for its potential impact on process-related impurities derived from cell substrates (Host cell protein (HCP), host cell DNA). These are controlled on AS level and are part of the AS specification.

Additionally, results presented for the PPQ batches show that all process and product related impurities are effectively reduced through purification process.

Evaluation of the removal of process related impurities was also performed on spiking clearance study. Qualified scale down model is used and assessed as appropriate. Spiking studies are performed in a way that each unit operation is separately loaded and assessed for reduction of each impurity. From the data provided, it can be seen that even with the high load, downstream process is capable of reducing impurities as HCP, DNA, HMWS, hydrophobic variants and charge variants to acceptable level.

For other process-related impurities derived from reagents used through the manufacturing process, i.e. media components, a table presenting risk assessment of criticality of each impurity is given. Clearance study to confirm no safety concerns like immunogenicity or toxicity in regard to critical process derived impurities are provided. Also, toxicity/immunogenicity/safety risk assessment with presented expected amount of critical process-related impurities in FP dose and safety evaluation limits are provided. For both critical process derived impurities, it can be concluded that there is no safety risk.

Characterisation of product related impurities

Characterization of isolated size variants (LMW), charge variants (acidic, basic and main) and hydrophobic variants (pre and post peaks) was conducted to determine their identity. Additionally, biological activity for FP under different stressed conditions was also analysed.

Comprehensive data on isolation and characterization for each variant of product related substances/impurities is provided. Since low level of product related impurities can be found in FP, forced degradation conditions (low pH, high pH, thermal stress and oxidation with H_2O_2) were used to induce formation of different variants.

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a humanised recombinant IgG1-type Fab fragment antibody. The analytical results are consistent with the proposed structure. In summary, the characterization is considered appropriate for this type of molecule.

3.2.3. Specification

As per Ph. Eur. monograph "Monoclonal antibodies for human use" the AS is tested for appearance (colour and opalescence), pH, osmolality, identity, protein content, potency (biological activity by cell bioassay and binding by ELISA) product - related substances and impurities (molecular-size distribution by SE-HPLC and reduced and non-reduced CE-SDS, hydrophobic variants, charge variants), process - related substances, bioburden and bacterial endotoxins, as well as excipient (polysorbate 20). For molecular identity peptide mapping and VEGF-A165 binding by ELISA is employed.

Ph. Eur. recommends test on process-related impurities on AS, and these are tested on routine level (HCP, DNA). Concentration of polysorbate 20 is included in AS specification for release and stability/shelf life. The approach is endorsed.

A binding ELISA assay and inhibition of proliferation in HUVEC cells - cell based assay are included for potency. For Purity, adequate tests to control the product related impurities as such are included.

The methods used are either Ph.Eur. or in-house methods for which unique identifiers/in-house method numbers are listed in the specification**.**

Specifications are listed with acceptance criteria valid for release and for stability. The stability specification for ranibizumab AS comprises a reduced set of parameters: osmolality, identity, process-related impurities are not monitored. Since no change is expected for these parameters, this is acceptable. For size variants by nrCE-SDS and rCE-SDS, and hydrophobic and charge variants testing as well as for Polysorbate 20 the wider criteria is applied for stability. The proposed acceptance criteria for QAs in AS specification are considered acceptable.

In principle, a sound and comprehensive panel of assays for routine release testing (in accordance to Ph.Eur. and ICH Q6B) is in place to ensure that only AS meeting predetermined quality requirements will be further processed to FP.

Analytical procedure

The analytical procedures used for testing the AS are provided. Compendial analytical procedures include colour, clarity, pH, osmolality, bacterial endotoxins and bioburden. Reference to relevant Ph. Eur. monographs is stated. For endotoxin, kinetic turbidimetric method is carried out for AS and gel-clot method is used for in-process samples. All other methods are non-compendial. A description of the methods is included.

Data about the methods used and/or changed during development are provided in the dossier.

Validation of analytical procedure

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines (ICHQ2 (R1).

The validation summaries are provided for all non-compendial methods, as well as respective validation reports. Method validation is performed on AS and/or FP samples, and for purity/impurity testing (SE-HPLC, RP-HPLC, IE-HPLC) additional validation is performed and on IPC samples, where applicable. It can be agreed that there is no practical difference between AS and FP that could impact validation results and conclusions, hence, the AS validation is applicable for FP, where appropriate. Some validations are also performed on reference standard as samples.

Batch analyses

Batch analyses data for multiple AS lots manufactured throughout development, at lab scale and at commercial scale and which are used for development, analytical assessment, stability, representative of clinical batches, clinical trials (Phase I and III), reference standard establishment, process validation and post-process validation are provided.

All presented batches met the acceptance criteria used at the time of testing. The batch analysis data presented for the PPQ and post PPQ batches comply with the parameters and limits as proposed in the AS specification. The data demonstrate that commercial process is capable of manufacturing an AS of consistent quality.

The changes of AS specification in parameters and acceptance criteria made during development are also presented.

Justification of specification

The applicant states that the ranibizumab AS release and stability specification is set based on historical data, stability information, clinical experience, process and product characterisation and acceptable safety limits. The applicant states that AS specification are based on batches produced through a commercial scale process with the stability data considered.

Data sets (batch number and result of testing) used to establish the acceptance criteria are indicated for each parameter.

For protein content, the AS acceptance criteria is set tighter than for FP acceptance criteria to have more stringent control.

The AS release acceptance criteria for the potency, as well as purity and product related impurities were derived from statistical evaluation of the quantifiable values.

The acceptance criterions for potency, by *in vitro* cell-based assay and *in vitro* binding of VEGF-A165 by ELISA, are explained and supported by data.

For Polysorbate 20, the batch release and stability data is taken into account for setting the acceptance criteria. For the AS shelf-life, the acceptance criterion is widened and is set taking into account the highest observed AS and FP release values, highest observed FP stability value, proposed AS release upper limit and difference related to analytical variability. The same acceptance criterion as for AS shelf life is also set for FP release and shelf life. The applicant also committed to further evaluate approaches to decrease the variability observed during analysis. This is reflected as recommendation (REC).

Overall, the approaches used and acceptance criteria set are considered adequate to ensure that only AS meeting predetermined quality requirements will be further processed to finished product.

Reference standards

To date, three reference standards have been produced: developmental IRS/Ranibizumab/15/001, interim reference standard IIRS/010/19/001 and one in-house primary reference standard IPRS/010/22/001. The applicant states that both interim standard and primary standard originate from lots that accurately reflect production and clinical materials. The date of manufacture of each of reference standard is stated**.**

IPRS was used in the biosimilarity exercise and will be used to qualify in-house secondary reference standards in the future and until the secondary standard is qualified it will be used for the batch release and stability testing. This is considered appropriate.

It is stated that IPRS was qualified against IIRS/010/19/001, which is considered adequate. Also, the applicant states that AS batches used to produce IPRS individually comply to the approved AS specification.

In addition to batch release results, characterization studies were also performed. The panel of characterization data is considered adequate. Results of characterization studies show that IPRS and IIRS are comparable.

Stability testing of IPRS is scheduled for every 6 months till 24 months and yearly thereafter for physicochemical parameters while for potency testing is scheduled every 6 months and IIRS will be used as reference standard. This is considered appropriate. Stability data are presented and the results are within stated acceptance criteria and show that IPRS is stable at stated storage conditions.

Qualification of future primary reference standards and in-house secondary reference standards (ISRS) is described. The proposed qualification protocol consists of release and characterisation testing and is considered acceptable.

For the in-house secondary reference standards, the applicant states that the first and subsequent ISRS will be established with reference to the IPRS valid for use at that time. Once the first ISRS is established, it shall be used for lot release, stability testing, and other analysis (analytical purpose) as required for the AS and FP. The applicant also states that FP to establish ISRS is already chosen. The results of qualification of ISRS are provided.

Container Closure System

The manufacturer of the CCS components is indicated. The applicant has provided sufficient data on the CCS, including a description of its components, specifications with representative certificate of analysis, and technical drawings with critical dimensions, in line with ICH M4Q(R1). Compliance of the CCS components with relevant Ph. Eur. monographs is confirmed.

Results of extractable and leachable studies are provided. The assessment indicates that there is no risk to patient safety due to potential leachable from container closure systems in AS under the defined storage conditions of use. The provided data are acceptable.

3.2.4. Stability

The proposed shelf life of ranibizumab AS, when stored at the recommended temperature, is considered acceptable.

To support the shelf-life claim, stability program is designed in accordance with ICH stability guidelines. Stability data have been provided for long-term conditions (-20 ± 5 °C) up to 48 months, accelerated conditions (5.0 ± 3.0 °C) up to 6 months, and additionally for stress studies (25 ± 2°C,

60.0 ± 5.0% RH) up to 28 days, and freeze-thaw study (thaw at 5 ± 3ºC or 25 ± 3ºC) up to 2 days/5 cycles.

Real-time stability results up to 48 months have been provided for developmental and clinical batches, while 24 months of ongoing stability are available for PV batches. The 6 months accelerated study has been completed for all tested batches. All available stability results met the acceptance criteria for all tested CQAs under all tested conditions throughout the proposed shelf life, with no observed significant trends or significant changes. Results from the thermal stress study demonstrated that the AS remains stable at 25 ± 2°C, 60.0 ± 5.0% RH for 14 days. The freeze-thaw study results support up to five freeze-thaw cycles when thawed at 5 ± 3ºC or 25 ± 3ºC, and also when held up to 2 days at 25 ± 3ºC or 5 ± 3ºC after thawing.

Developmental AS stability batches and PV batches were included in the selection of batches. These batches were stored in containers representative of the AS manufacturing-scale container. Taking into account that comparability of AS batches from pre-clinical, clinical and PV/commercial manufacturing process is demonstrated, the provided stability batches can be considered representative of the commercial manufacturing process.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

The post-approval annual stability protocol is considered acceptable.

3.3. Finished Medicinal Product

3.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is a clear to slightly opalescent, colourless to pale brownish aqueous, preservative-free solution for IVT administration, containing 10 mg of Ranibizumab in 1 mL of solution. Other ingredients are: α,α-trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20 and water for injections.

It is presented as a single-use Type I glass vial (2.3 mg/0.23 ml) or as a single-use PFS (1.65 mg/0.165 ml). The excipients are the same as that of the reference product Lucentis and they are of compendial quality. There are no novel excipients, and no excipients of human origin. Trehalose is produced through microbial production using raw materials derived from bovine milk.

AS is supplied at a target concentration 10 mg/mL in the final formulation and no additional dilution/formulation is performed during manufacture of FP.

The target fill volume is set at 0.23 mL and 0.165 mL for vial and PFS presentation respectively. There is an overfill in the vial and syringe presentations compared to the volume required to deliver the appropriate dose. These overfills (similar to the reference product) have been justified in both cases as the minimum volumes (extra volume to aid priming the needle and syringe in preparation for the injection) required in order to consistently achieve accurate dosing and the fill volume does not allow preparing 2 doses.

The FP does not contain any overages.

Formulation development

Formulation buffer development and optimization included several studies. Weighing method was

selected as preferable method for preparation of formulation buffer. The effects of varying concentrations of histidine buffers and trehalose were evaluated. The effect of pH range on ranibizumab stability was evaluated. The formulation excipient ranging study was performed in order to optimize the formulation preparation.

Manufacturing process development

FP manufacturing process was designed based on process and product understanding, prior experience with similar product presentation and process characterization studies. FMEA was performed to identify the risks associated with each manufacturing step. Characterization studies were initiated to evaluate the effects of manufacturing steps on FP quality.

Presented manufacturing process developmental phase consisted of optimization studies for the process parameters such as thawing time, mixing time, mixing speed, hold time of AS after thawing and mixing, filtration flow rate, filter surface area, filling velocity and filing needle in-process hold.

Comparability

The process development is presented in two phases: developmental phase and process validation phase.

Developmental vs. clinical batches (developmental phase)

A comparative overview of manufacturing processes is provided. Differences between processes entail increase in AS container capacity, use of different filter membrane for 2 clinical batches, introduction of 1st filter post-use integrity testing and 2nd filter pre- and post- use integrity testing. The introduced changes can be considered as process improvements. The FP release specification results for all batches were presented and within acceptance criteria.

Clinical vial batches and PPQ vial batches comparability

A comparative overview of manufacturing process of PPQ and clinical batches for FP vial presentation is provided. FP fill-finish manufacturing process was transferred from clinical site to commercial site and was consequently scaled-up. In the case of clinical batches both filtration steps were performed offline, while in the case of PPQ batches, 2nd filtration was performed online. Another manufacturing difference can be observed at filling step. In the case of filling of filtered bulk in vials, for clinical trial batches this step was performed by piston pump in ORAB filling machine, while in the case of PPQ batches it was performed in isolator based advanced filling machine with check-weigher system. Vial sealing is performed on different equipment, as well. Equipment's parameters were adjusted to scale-up. A comprehensive comparability exercise was presented covering the establishment of comparability ranges derived from clinical-process batches, comparability across process stages, release and stability attributes, and extensive physicochemical and biological characterization. The mean ±3SD was applied to define the comparability ranges. In-process parameters were compared against the pre-defined process ranges while in-process QAs and QAs at release were compared against the comparability ranges. An extensive physicochemical and biological characterization panel used to demonstrate the process comparability included comparison of secondary, tertiary and higher order structure, comparison of functional attributes and product attributes. All characterization tests yielded comparable results. The comparability of stability trend under real time, accelerated and stress conditions was provided and found comparable and within acceptance criteria. Based on the information provided, it can be concluded that clinical vial batches and PPQ vial batches are comparable.

Vial and PFS comparability

A comparative description of batch size and unit operations for both vial and PFS presentations is

provided. In comparison to the vial, differences in PFS manufacturing process are related to specific demands regarding PFS device components.

Comparison of FP composition and manufacturing process between vial and PFS FP presentations was provided. The comparability between FP in vials and PPQ PFS batches was performed with respect to process stages, release attributes, stability attributes and extensive physicochemical and biological characterization. For establishment of comparability ranges, data from available clinical vial batches were used. The comparability ranges were defined as mean ±3SD. In-process parameters were compared against the pre-defined process ranges while in-process QAs and QAs at release were compared against the established comparability ranges (with the exception of the extractable volume and PFS functionality test). Due to use of PFS filling machine, the main differences between two processes are observed in filling step. Based on the consistency observed for process parameters and QAs, the comparability between PPQ PFS and clinical manufacturing process can be concluded for all presented process steps except for PFS specific filling step. Also, an extensive physicochemical and biological characterization panel is used to demonstrate the process comparability. In order to compare AS batches corresponding to pre- and post-change FP batches, AS lots corresponding to clinical trial batches and AS lots, corresponding to PPQ PFS lots were compared. All characterization tests showed comparable results. Stability studies are still ongoing, but the available real-time, accelerated and stress stability data demonstrates that the results remain within predefined acceptance criteria. Based on the information provided, it can be concluded that clinical vial batches and PPQ PFS batches are comparable.

Container closure system (development)

The primary container closure system for FP vial is composed of a Ph.Eur./USP 2R Type I glass vial with a 13 mm fluorotech coated brombutyl rubber stopper and 13 mm aluminium body flip-off seal.

The vials used in clinical studies were pre-sterilized (ETO), while the vials used for PPQ batches and for commercial batches are not pre-sterilized. There are no other differences between these vials. The assessment of impact of multiple freeze-thaw cycles on quality of FP in vial demonstrates that FP frozen at -20 ±5°C in Ph.Eur./USP type I vial is stable up to 5 freeze-thaw cycles when thawed at 5 ± 3 °C or 25 ± 2 °C.

The single-use type-1 glass vial is similar to the EU-approved or US-licensed Lucentis.

The primary container closure system for FP PFS is made of cyclo olefin polymer (COP). The selection of PFS was based on the comparative evaluation of 0.5 mL syringes made of COP which were procured from three different manufacturers. The compatibility studies for these three COP PFS addressed FP impurity profiles under thermal stress, photo stress and freeze thaw stress conditions. Based on the obtained performance data, COP PFS was selected. The applicant provided physical comparison of the Delivery Device Constituent Parts between reference Lucentis PFS and Lupin PFS. Method validation reports for the functionality tests are provided.

The microbiological attributes are evaluated by sterility testing, bacterial endotoxin testing, bioburden testing and container closure integrity tests (CCIT).

The compatibility of several contact parts used in FP manufacturing was assessed. The summarized data indicated no adverse effects on the specific QAs of the FP matrix. The extractables and leachables risk assessment was conducted on product-contact manufacturing components.

Overall, the choice of the container closure system is adequate for the intended use of the product.

3.3.2. Manufacture of the product and process controls

Name, address, and responsibilities of manufacturers involved in the manufacture, control and batch release of FP are listed.

Valid GMP certificates covering the indicated responsibilities for the sites involved are provided. Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

Description of the manufacturing process and process controls

The composition of FP and AS is the same. The FP manufacturing process comprises the filling of AS into 2 mL vial and 0.5 mL PFS.

Concentration of AS used for filling vial and PFS is the same (10 mg/mL), the only difference is in the fill volume. The AS is fully formulated, and ready-to-fill solution supplied in containers that are stored at defined temperature.

The FP manufacturing process is divided in two parts. The first part includes thawing and mixing of AS, pooling and mixing of AS, filtrations and filling operations. The vials and syringes are aseptically filled and stoppered using rubber stopper and plunger stopper, respectively and then subjected to visual inspection. The second part of manufacturing process includes the secondary packaging operations like flip-off seal (vial) and plunger rod assembly (PFS), labelling, final packaging of vials, blister packaging of PFS, surface sterilization of PFS blister packs and final packaging of surface sterilized PFS. Given that LUBT010 is sensitive to light, all fill-finish and packaging operations are conducted under controlled light conditions.

For both FP presentations, flow diagrams of the manufacturing processes and descriptions for all steps including CPPs and IPCs are provided. Proposed hold times for both presentations of FP have been established. The filtration and filling time is controlled with CPP total filling time.

Control of critical steps and intermediates

The manufacturing process controls are described. A subset of performance indicators was designated as IPCs for routine manufacture and they are controlled by acceptance criteria/action limits. In addition to IPCs, in-process checks carried out during filling, stoppering and sealing steps are described, as well. Process parameters are categorized as CPPs or non-CPPs and their limits/operating ranges provided with accompanied justifications. For PFS surface sterilization procedure, PPs with operating ranges are provided, as well.

The methods used for release and in-process testing are the same except for bioburden and PFS blister pack integrity tests. The descriptions of these methods are provided in the dossier. The bioburden test by membrane filtration method, as outlined in Pharmacopoeia standards, is employed for in-process testing of samples obtained from the pooling and mixing of AS and prior to 2nd sterile online filtration. PFS blister pack integrity is tested with dye injection method which is, according to the American Society for Testing and Materials, standard test for detecting seal leaks in porous packaging by dye penetration (ASTM F1929).

Process Validation

Process validation of FP manufacturing process was performed for consecutive FP vial batches and consecutive FP PFS batches. Different combinations of different AS lots were used to manufacture independent FP batches. A summary on the performed PPQ included the process and performance parameters per manufacturing step for each of FP vial/PFS batch.

Validation was made for PPs for all process steps, including packaging in-process checks for vial, and

NO2 surface sterilization (for PFS). In case of PFS filling and stoppering step, CCS integrity was checked by leak test and blister pack integrity test and IPC visual inspection was performed.

In the case of all PPQ FP batches, QAs complied to IPC, IPT and release acceptance criteria. In general, process parameters performed within set operating ranges/standard limits.

Sterile filter validation

The filter validation studies comprised of filter compatibility study, filter integrity testing with AS (as wetting fluid), bacterial viability and bacterial retention study, and filter extractable study. The summary of filter validation studies was provided with accompanying validation reports attached. The data provided is considered acceptable.

Hold time validation

Three hold times were proposed for commercial manufacturing process; unfiltered bulk solution hold (NMT 24 hrs), filtered bulk solution hold (NMT 48 hrs) and filled vials/PFS hold at room temperature (NMT 24 hrs). The validated hold times are based on data demonstrating the maintenance of product quality and microbial control within the proposed hold times.

Aseptic process validation

Validation of aseptic processing was performed in one run for vial presentation (requalification) and in three runs for PFS (initial qualification). Results demonstrated that aseptic conditions were maintained during filling. Media fill study reports are provided, and overall, sufficient information has been provided.

Container closure system sterilization

Sufficient information has been provided on qualification of the vial depyrogenation and steam sterilization of rubber stoppers. Periodic qualification reports for both methods are provided. PFS surface NO2 sterilization was validated and the process qualification protocol is provided. Optimization and development of PFS surface sterilization step is adequately described in manufacturing development section.

Shipping validation

The shipping validation studies were designed to verify that the recommended storage condition (2–8°C) was maintained throughout transportation. A brief summary of the shipping validation studies for both FP presentations has been provided, and the results were found to be acceptable.

Control of excipients

All the excipients are of compendial origin, routinely used in parenteral formulations. There are no novel excipients used. The information provided is considered acceptable.

Overall, the manufacturing process has been validated. The in-process controls are adequate. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

3.3.3. Product specification

As per Ph. Eur. monograph "Monoclonal antibodies for human use" the FP in both presentations (vial and PFS) is tested for appearance (colour, clarity, visibility), pH, osmolality, identity, extractable volume, protein concentration, molecular size distribution, molecular identity and structural integrity, purity (product-related substances and impurities), potency - biological activity by suitable analytical methods

(cell based and binding), concentration of polysorbate 20, sterility and bacterial endotoxins. Additionally, tests for particulate matter/sub-visible particles is also part of the FP specification (vial and PFS).

Molecular and structural identity are confirmed using peptide mapping with RP-HPLC. Peptide mapping RP-HPLC and VEGF-A165 binding ELISA are stated as identity test. Taking into account that potency assay can also serve as surrogate assay for identity determination, this is considered acceptable. Container closure integrity is also part of the FP specification (both presentations) which is acceptable.

Some additional parameters are stated for the FP PFS specification only: break loose force (BL), gliding force (GF) and torque force, which is considered acceptable. There is also a difference between FP vial and FP PFS specification in test performed for CCIT.

Overall, with the exception of few tests only conducted at FP release (visible particles, volume, particulate matter, sterility, CCIT, BL, GF, Torque force) all test parameters are identical between AS and FP release.

The methods used are either Ph.Eur., USP or in-house methods for which unique in-house method numbers are listed in the specification.

Acceptance criteria for stability testing/shelf life, where different from release have been detailed. The stability/shelf-life acceptance limits for potency by cell assay, purity (nrCE-SDS, rCE-SDS, RP-HPLC and IE-HPLC) are different from the release specification limits.

A sound and comprehensive panel of parameters for routine release testing (in accordance to Ph.Eur. and ICH Q6B) is in place.

Characterisation of impurities

The applicant states that impurities are evaluated on AS level and that only additional impurities on FP level that needs to be evaluated are bacterial endotoxins which are part of FP release testing.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that the risk for elemental impurities is negligible. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical procedures

Some of the analytical methods are the same for AS and FP, and all analytical methods are the same for both FP presentations (PFS and vial) (except where parameter is not applicable).

Ph, Eur. methods are: colour, clarity, pH, osmolality, particulate matter (visible and subvisible), extractable volume, bacterial endotoxins and sterility. For PFS functionality testing reference to ISO standard is given.

Validation of analytical procedures

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

According to the provided table all compendial methods used to test FP are verified for their intended use. Presented results in the provided summaries confirm that methods are successfully transferred since the results are within the preset criteria. The applicant provided validation reports as well as summaries of the transfer of the methods validation.

Batch analyses

The batch analyses data for FP lots used through development, as developmental batches, representative clinical batches, batches used in clinical trials and process validation batches are provided. Overall, the batch analyses results of FP batches for vial presentation and for PFS presentation are presented.

The changes of FP specification in parameters and acceptance criteria made during development are also presented.

Results for all presented batches met the acceptance criteria used at the time of testing. The batch analysis data presented for the PPQ batches comply with the limits proposed in the FP specifications. The data demonstrate that commercial process as presented is capable of manufacturing finished product of consistent quality.

Justification of specification(s)

The applicant states that the FP release and stability specification is set taken into account historical data, stability information, clinical experience, process and product characterisation and acceptable safety limits. The applicant states that FP specifications are based on batches produced through a large-scale process with the stability data considered.

Data sets (batch number and result of testing) used to establish the acceptance criteria are indicated for each parameter and differ between parameters. For some parameters results of large number of batches were considered and are presented for setting the acceptance criteria, while for others only small number are presented and taken into account. Since comparability between all different process versions (batches linked to those processes) is confirmed on AS and FP level this is considered acceptable.

The FP release specification acceptance criteria was kept the same as AS shelf-life acceptance criteria as no manufacturing step except thawing and mixing is involved between AS to FP.

The acceptance criterion for Visible particles and sub-visible particles is stricter than Ph. Eur. and in align with USP and considered acceptable.

Overall, the acceptance criteria set are considered adequate.

Reference standard

Reference standard used for finished product testing is the same as for the active substance.

Container Closure System

VIAL

The packaging components include Type I glass vial, FluroTec coated bromobutyl rubber stopper, and 13 mm flip-off seal made of aluminium body with polypropylene top. The test procedures for vials, rubber stopper and flip-off aluminium seal are provided including representative in-house and vendor Certificate of Analysis. Specifications for all components of CCS are provided, including technical

drawings and dimensional characteristics. Specifications for glass vial comply to Ph.Eur.3.2.1. and for rubber stopper to Ph.Eur.3.2.9.

Regarding extractables and leachables, it can be concluded that the risk can be considered as low.

PFS

The packaging components include a syringe made of cyclo olefin polymer (COP) with dose mark and luer lock, plunger stopper made by chlorinated butyl rubber with i-coating and plunger rod made of polypropylene. The i-coating stopper technology eliminates the need for silicone oil in the syringe system.

The test procedures and representative in-house and vendor Certificate of Analysis are provided, along with specifications and technical drawings with dimensional characteristics. The packaging material is supplied sterilized. The sterilization is performed by device manufacturer.

Components of packaging material, a syringe barrel with luer lock and tip cap, and plunger stopper are in direct contact with FP. Extractable/ leachable studies were performed and the protocol is provided.

According to the Article 117 of the Medicinal Device Regulation (EU) 2017/745 (MDR), a Notified body opinion on the conformity of the integral device part with the relevant general safety and performance requirements set out in Annex I of the MDR is provided.

3.3.4. Stability of the product

Vial

The stability studies for FP vial presentation included developmental batches, developmental clinical scale batches, clinical batches (phase III clinical trial) and PPQ batches. The Type I glass vials used as CCS in clinical studies were pre-sterilized (ETO). The vials used for PPQ batches are not pre-sterilized and they are depyrogenated by validated process during manufacturing.

In the case of developmental batches, vials were stored in both inverted and upright position for testing in all three thermal conditions. For these batches stability data up to 48 months at the long-term storage condition (5°C±3°C), 6 months at accelerated conditions (25°C±3°C) and 28 days at stress conditions (40°C±2°C) are available and show no significant changes during duration of the studies.

For clinical batches stability data up to 48 months at the long-term storage condition is available and all tested CQAs met the acceptance criteria. For PPQ batches real-time stability data are available. At accelerated condition, stability for all PPQ batches is completed. All available stability results indicate that PPQ batches are stable under investigated conditions.

The applicant proposes a shelf-life of 36 months for FP vial when stored at 5°C ± 3°C. Proposed shelf life is considered acceptable, as 48-month real-time stability data and accelerated stability data are available for clinical batches (clinical scale development batches and clinical batches) which were also included in the comparability exercise to support the comparison between the clinical batches and the PPQ vial batches. All provided results indicate these clinical batches to be stable under investigated conditions. The applicant commits to continue real-time stability study for the process validation batches for the proposed test period of 42 months.

PFS

FP PFS PPQ batches *without surface sterilization* have completed 12 months stability testing at long-term storage condition, as well as the planned accelerated and stress stability studies, and were found

to be stable. For the same PPQ PFS batches *with surface sterilization*, stability studies are still ongoing, except for stress stability study which is completed. The applicant claims shelf life of 12 months for FP PFS when stored at 5°C ± 3°C, which was considered acceptable. The real-time stability study will be continued for the proposed test period.

The photostability study performed in the case of both FP presentations showed that FP is sensitive to light exposure. The study further demonstrated that secondary packaging provides effective protection from photo exposure and that FP photostability can be maintained under commercial manufacturing conditions.

Based on available stability data, the shelf-life of 3 years (vial) or of 1 year (PFS), at 2°C -8°C, as stated in the SmPC, are acceptable.

3.3.5. Comparability exercise for finished medicinal product

A comprehensive analytical similarity study was planned and performed by the applicant for the purpose of demonstration of biosimilarity at the quality level between the proposed biosimilar product and EU sourced Lucentis reference medicinal product (RefMP). The biosimilarity exercise included comparative analytical assessment and stability studies to compare degradation profiles.

The applicant presented its risk based CQAs ranking approach based on which analytical biosimilarity evaluation plan has been designed. The risk ranking approach and CQA categorization are described in sufficient detail and presented very clearly. The justification for risk / criticality score is given and endorsed.

In addition, the applicant took into account advice on biosimilarity plan given in previous scientific advice procedure.

Based on criticality score of each attribute, approach for evaluation of biosimilarity is defined (quality range approach for quantitative attributes of very high, high and moderate risk; graphical or spectral comparison for qualitative attributes or attributes with low risk). This means that qualitative attributes of low risk were just compared without any pre-defined biosimilarity range. Approach is acceptable since it is acceptable that low risk attributes are tested with fewer number of batches and in this case, range setting is not meaningful. In addition, most of these data clearly indicate similarity.

To establish biosimilarity ranges, the applicant used different approaches in dependence of quality attribute, its criticality, and data distribution. Limitations in availability of RefMP batches are acknowledged and number of batches used for establishing of the ranges is in principle acceptable. In addition, biosimilarity results are clear, especially for CQAs. Hence, biosimilarity ranges are considered acceptable and derived in line with EU guidelines. The comparative analytical assessment study was performed across three analytical campaigns. This approach is acknowledged.

Selection and number of batches

The applicant has presented summary tables of all batches of reference medicinal product and biosimilar, used in the biosimilarity exercise including relevant details as per EMA/CHMP/BWP/247713/2012 (pharmaceutical form, strength, batch number and age of the batches). For some of the Lupin batches used for biosimilarity exercise, purpose and use is indicated. Since comparability between different developmental manufacturing process materials is demonstrated, use of all batches independently of manufacturing process used to produce them, is acceptable to be combined in one biosimilarity exercise.

EU RefMP batches (vials and PFS) was used spanned different ages within the shelf life of 36 months.

For the biosimilar, AS batches and FP bathes (only for protein concentration and sub-visible particles assessment, have been used, spanned different ages within the shelf life of 42 months for AS. Age of the batches at the time of use in biosimilarity is provided and reflects appropriately FP shelf life.

Inclusion bodies independent AS batches were mostly used and FP batches used for biosimilarity were manufactured mostly from different AS batches. This approach is supported since it allows for more meaningful evaluation without data duplication.

Use of mostly AS batches of the biosimilar for biosimilarity exercise is justified by the applicant with no additional steps except for filling at the FP level after AS thawing and with results of comprehensive comparability study between AS and FP. This is endorsed.

Number of the batches used for comparison of each attribute is indicated and is higher for critical quantitative QA and lower for less critical QAs. This is in general supported and allows for meaningful statistical evaluation of similarity of a critical quality attribute.

Some of the RefMP and biosimilar batches were frozen before use in biosimilarity exercise or in comparative forced degradation study, to avoid shelf-life expiration before analysis. Although this approach is usually discouraged, it is acknowledged that low temperatures should not have significant impact on recombinant monoclonal antibody proteins quality. Results of the freeze thaw study using RefMP Lucentis and biosimilar product have been provided. In this study, samples were frozen at ≤-70 °C and thawed at room temperature (~ 25° C) for 3 freeze thaw cycles and analysed to check impact on different physicochemical and functional attributes. Choice of tests to analyse impact of freezing and thawing is endorsed and it can be concluded that unchanged quality of RefMP batches used in analytical biosimilarity exercise has been confirmed after freezing and thawing.

Biosimilarity analytical panel and analytical methods

A comprehensive panel of analytical tests was used for the analytical biosimilarity exercise, which included orthogonal methods that measure different aspects of the same CQAs. The test panel is comprised of both, release and characterization assays. Panel covers primary, secondary, tertiary and higher order structure, product related impurities, potency and biological activity as well as product related attributes (protein content and sub-visible particles). Analytical panel is mostly same as proposed and evaluated as adequate during pre-authorisation scientific advice procedure. Advice given to include orthogonal method for aggregates and to detail the purpose of RP-HPLC has been taken into account by the applicant. In conclusion, analytical panel utilised for biosimilarity is considered appropriate. All methods used for biosimilarity are either validated or qualified / fit for the intended purpose. Summaries of method validation / qualification are provided in support to this claim.

Results

Summary of the results are provided.

Table 3: Analytical similarity assessment between Vislyfa and RefMP Lucentis

Molecular parameter	Attribute	Methods for control and characterisation	Key findings during Analytical similarity assessment between Vislyfa and RefMP Lucentis
Product-related Structural attributes			
	Amino acid sequence	LC-MS	Identical primary amino acid sequence
	Amino acid composition	UPLC	Proportion of different amino acids of Ranibizumab is similar in both products
	Peptide mapping (reducing)	UV detection,	Identical peak profiles
		SDS-PAGE (Non-reducing)	Similar position of principal band in both products

Molecular parameter	Attribute	Methods for control and characterisation	Key findings during Analytical similarity assessment between Vislyfa and RefMP Lucentis
Primary structure	Protein band patterns and molecular weight of the protein.	SDS-PAGE (reducing)	Similar position of HC and LC bands in both products
		Western blotting	Detection by anti-Ranibizumab antibody confirms identity of both products
	Intact mass and reduced mass analysis by	LC-MS	Observed Comparable masses
	Extinction coefficient (EC) determination	Edelhoch method	Comparable EC
Secondary structure	Structural comparison	Far UV CD spectroscopy, FTIR	Passed the qualitative (visual) and quantitative (quality range, two-sided comparison) criteria, and can be concluded as Lupin Ranibizumab highly similar to Lucentis EU.
Tertiary structure and Higher Order Structure Higher Order Structure	Structural comparison	Near UV CD spectroscopy, Intrinsic fluorescence spectroscopy, free thiol content, DSC, NMR spectroscopy	
	Comparison of a/b ratio	Second derivative UV spectroscopy	Comparable a/b ratio
	Disulfide bond analysis	LC-MS	Identical disulfide bonding Patterns
Product-related Functional attributes			
Potency	VEFF-A165 Potency	Neutralisation of VEGF-A165-mediated proliferation in HUVEC	Potency of Lupin Ranibizumab is similar to that of Lucentis EU for neutralisation of VEGF-A165-mediated proliferation in HUVEC assay.
		VEGF-A165 Enzyme Fragment Complementation assay using HEK293-KDR/KDR cells	Potency of Lupin Ranibizumab is similar to that of Lucentis EU for VEGF-A165 Enzyme fragment complementation assay usingHEK293-KDR/KDR cells.
	VEGF-A121 potency	VEGF-A121 Enzyme Fragment Complementation assay using HEK293-KDR/KDR cells	Potency of Lupin Ranibizumab is similar to that of Lucentis EU for VEGF-A121 Enzyme fragment complementation assay usingHEK293-KDR/KDR cells.
	VEGF-A110 potency	VEGF-A110 Enzyme Fragment Complementation assay using HEK293-KDR/KDR cells	Potency of Lupin Ranibizumab is similar to that of Lucentis EU for VEGF-A110 Enzyme fragment complementation assay usingHEK293-KDR/KDR cells.
	VEGF-A145 potency	Neutralisation of VEGF-A145-mediated proliferation of HUVEC	Potency of Lupin Ranibizumab is similar to that of Lucentis EU for neutralisation of VEGF-A145-mediated proliferation in HUVEC assay.
	VEGF-A189 potency	Neutralisation of VEGF-A189-mediated proliferation of HUVEC	Potency of Lupin Ranibizumab is similar to that of Lucentis EU for neutralisation of VEGF-A189-mediated proliferation in HUVEC assay.
ligand binding	VEGF-A165 binding	VEGF-A165 binding assay by ELISA	Binding activity (potency) of Lupin Ranibizumab DS is similar to that of Lucentis EU for VEGF-A165, VEGF-A121, VEGF-A145, VEGF-A189, VEGF-A206, VEGF-B, VEGF-C, VEGF-D, PlGF-1, PlGF2.
	VEGF-A165 binding	VEGF-A165 binding assay by SPR	
	VEGF-A121 binding	VEGF-A121 binding assay by SPR	
	VEGF-A110 binding	VEGF-A110 binding assay by SPR	
	VEGF-A145, VEGF-A189, VEGF-A206 binding	VEGF-A145, VEGF-A189, VEGF-A206 binding assays by SPR	
	VEGF-B, VEGF-C, VEGF-D, PlGF-1, and PlGF2 binding	VEGF-B, VEGF-C, VEGF-D, PlGF-1, and PlGF2 binding assays by SPR	

Product-related Variants			
Size Variants	Aggregates including dimer and other HMW species	SE-HPLC, SEC-MALS, AUC	Lucentis EU and Lupin Ranibizumab batches have similar levels of aggregates/HMW species Also, the main peak purity is similar between both products.
	LMW Fragments/ Truncated Fab	CE-SDS (Non-reducing and reducing), SE-HPLC	Lucentis EU and Lupin Ranibizumab batches have similar levels of LMW species. Also, the main peak purity is similar between both products.
Charge Variants	(Acidic and basic isoforms), Isoelectric point (pI)	Strong IE-HPLC, icIEF	Lucentis EU and Lupin Ranibizumab batches have similar levels of acidic and basic charge variants as well as similar isoelectric point.
Related Proteins	Hydrophobic variants,	RP-HPLC	Lucentis EU and Lupin Ranibizumab batches have similar levels of pre-peak and post-peak hydrophobic variants. Also, the main peak purity is similar between both products.
Post-translational modification	Oxidized variants	Peptide mapping by LC-MS	The total % oxidation was similar in Lucentis EU and Lupin Ranibizumab.
	Deamidated variants		The total % deamidation was similar in Lucentis EU and Lupin Ranibizumab.
	Acetylation		Acetylation is not detected in both products
	Methylation		N-terminal methylation of HC or LC is not observed in both products
Norleucine and Norvaline Incorporation	Composition	UPLC	Norleucine is not detected in both products Norvaline is below the limit of quantitation in both products.
Drug product-related attributes			
Protein Content		UV absorbance at 280 nm	Protein content of Lupin Ranibizumab DS and DP is similar to that of Lucentis EU
Sub-visible particles		Microflow Imaging (MFI)	Similar sub-visible particle concentration observed in Lucentis EU and Lupin Ranibizumab.

Results presented demonstrate high degree of comparability to RefMP Lucentis EU for all quality attributes.

The forced degradation study is performed as an extension to the analytical similarity assessment wherein degradation profiles of various presentations of the biosimilar and RefMP are compared under various stress conditions. Design of the study is considered adequate.

The samples were evaluated for hydrophobic, size, charge and functional attributes by RP-HPLC, SE-HPLC, CE-SDS (R and NR), IE-HPLC and VEGF-A165 ELISA, respectively, for the evaluation of the impact of stress condition on biological activity. Methods employed are stability indicating and endorsed.

Under all the stress conditions for the attributes tested with analytical panel described above, the results demonstrate similar degradation profiles of Vislyfa and EU-approved Lucentis. Thus, based on the comparative analytical assessment and forced degradation studies it can be concluded that Vislyfa is similar to EU-approved Lucentis.

3.3.6. Adventitious agents

All raw materials, consumables, and excipients selected for AS manufacturing are certified to be free from TSE/BSE. None of these materials are of human or animal origin, except for Trehalose. Trehalose is produced through microbial production using raw materials derived from bovine milk in the fermentation medium and complies with EMA/410/01-Rev 3. TSE/BSE certificates for raw materials, excipients, packaging materials, and AS and FP manufacturing are enclosed, and deemed acceptable.

Ranibizumab is expressed in an Escherichia coli (E. coli) host system, a commonly used substrate for biotherapeutics production with no reported safety issues related to viral contamination. Therefore, the risk of viral contamination is unlikely, and specific viral safety tests/viral validation studies are not performed. This is deemed acceptable.

3.4. Discussion on chemical, pharmaceutical and biological aspects

Vislyfa is developed as a ranibizumab biosimilar to the reference medicinal product EU-Lucentis. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Validation of manufacturing process is appropriately designed, in line with relevant guidelines and includes sufficient number of consecutive commercial scale batches. Process and product related impurities are identified. Stability studies have been performed in accordance with ICH guidelines and the proposed shelf life when stored at the recommended temperature are acceptable. The results of tests carried out indicate consistency and uniformity of product quality characteristics.

Formulation development and optimization included several studies, and the provided data are overall acceptable.

Comparability between the developmental and clinical batches was demonstrated. For the comparability between clinical and PPQ vial batches, and between clinical and PPQ PFS batches, comprehensive comparability exercises were presented.

The proposed release tests are in line with the expectations of ICHQ6B and the Ph. Eur. monograph on monoclonal antibodies and cover the identified CQAs.

For Polysorbate 20, the applicant also committed to further evaluate approaches to decrease the variability observed during analysis. This is reflected as recommendation (REC).

The proposed shelf life and the stability data provided are acceptable.

Adventitious agents safety is adequately covered.

An analytical similarity study was performed by the applicant for the purpose of demonstration of biosimilarity at the quality level between the proposed biosimilar and reference medicinal product (RefMP). Based on quality attributes criticality ranking approach, which is supported, evaluation plan has been adequately designed and appropriate statistical methodology utilised for comparison of critical quantitative attributes. A comprehensive panel of analytical tests was used for the analytical biosimilarity exercise, which included orthogonal methods that measure different aspects of the same CQAs. All methods used for biosimilarity are either validated or qualified / fit for the intended purpose. Results presented demonstrate high degree of comparability to RefMP Lucentis EU for all quality attributes. Thus, based on the comparative analytical assessment and forced degradation studies it can be concluded that Vislyfa is similar to EU-approved Lucentis.

Overall, it can be concluded that biosimilarity is considered demonstrated at the level of the quality.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety. Biosimilarity results presented indicate similarity between biosimilar Vislyfa and EU reference product Lucentis.

3.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Proposed list of recommendations

Description of Recommendation(s)
1. The applicant committed to further evaluate approaches to decrease the variability observed for polysorbate 20 method (REC).

4. Non-clinical aspects

4.1. Introduction

The applicant provided an adequate non-clinical developmental program applicable for ranibizumab.

Due to the applicable EMA Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) – it is stated, that "*If the comparability exercise in the in vitro studies is considered satisfactory and no factors of concern are identified, or these factors of concern do not block direct entrance into humans, an in vivo animal study may not be considered necessary*".

In vitro studies from comparability exercise between LUBT010 and EU-Lucentis were satisfactory, and no factors of concern were identified. Thus, no residual uncertainties were observed. However, Lupin has conducted an *in vivo* repeat dose toxicity study against India-Lucentis to meet the Indian regulatory requirement. Different countries follow different guidance and have different expectations regarding the need for *in vivo* animal studies in support of the non-clinical development of medicinal products.

This Repeated Dose (4-Week) Intravitreal Toxicity Study in Rabbit with 14 Day Recovery Period, was conducted GLP compliant.

4.2. Analytical methods

The *in vitro* testing for LUBT010 included cell-based assays and ligand binding covering the potency and primary target ligand.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Ranibizumab is designed for intraocular use, targeted against human VEGF-A. VEGF-A is a key factor mediating angiogenesis, binding of VEGF-A to its receptors lead to endothelial cell proliferation, and vascular leakage which contribute to progression of AMD. Among multiple isoforms generated from alternate splicing of VEGF-A gene, VEGF165, VEGF121 and VEGF110 are three predominant biologically active soluble isoforms in *in vivo*. Ranibizumab binds to all these three isoforms with high affinity. Thus, Ranibizumab neutralizes VEGF-A isoforms and precludes binding of VEGF-A to its receptor henceforth inhibiting activation of downstream signalling cascade which leads to advancement of AMD.

Based on the mechanism of action of ranibizumab, *in vitro* pharmacology testing was designed.

The *in vitro t*esting for LUBT010 included cell-based assays and ligand binding covering the potency and primary target ligand. Based on the provided results, the different VEGF-A binding activities (potency) of Lucentis EU and LUBT010 (performed with ELISA and by SPR) can be considered similar.

Furthermore, the potency of LUBT010 is similar to that of Lucentis EU for VEGF-A121 neutralizing activity in enzyme fragment complementation (EFC) assay using HEK293-KDR/KDR cells.

In addition, the *in vivo* comparability study did not demonstrate any meaningful differences between LUBT010 and Novartis Lucentis. However, the Lucentis product used in this *in vivo* study was marketed in India. Thus, as such it can't be regarded in support of the biosimilarity approach between LUBT010 and the EU-Lucentis product.

4.3.1.2. Secondary pharmacodynamics

No secondary PD studies were performed because no secondary pharmacodynamic effects would be anticipated with Lupin LUBT010.

4.3.1.3. Safety pharmacology

No dedicated safety pharmacology studies were performed for Lupin LUBT010 because these studies are not considered necessary for the registration of a biosimilar medicinal product.

4.3.1.4. Pharmacodynamic drug interactions

PD drug interaction studies are not necessary for registration of a biosimilar medicinal product. Therefore, no such studies were conducted for Lupin LUBT010.

4.3.2. Pharmacokinetics

No studies on PKs have been submitted for Lupin LUBT010, in accordance with the "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*" (EMA/CHMP/BMWP/403543/2010).

4.4. Toxicology

4.4.1. Single-dose toxicity

No dedicated single dose toxicity study was conducted in accordance with the "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*" (EMA/CHMP/BMWP/403543/2010).

4.4.2. Repeat-dose toxicity

A "*Repeated Dose (4-Week) Intravitreal Toxicity Study in Rabbit with 14 Day Recovery Period*" was conducted.

Groups of three rabbits of each sex were administered Lupin's LUBT010 by IVT injections made in each of the eyes, once in two weeks, for four consecutive weeks i.e. on days 1, 15 and 29. The treatment groups were accompanied by a concurrent vehicle (diluent) control group and a reference article (Lucentis) group of rabbits. The dose levels tested were 0.5 mg, 1 mg or 1.5 mg per eye, and were one, two and three multiples (1X, 2X and 3X) respectively of the clinical dose (in absolute terms) and employed the same absolute therapeutic dose volume of 50 µL.

The animals were observed for the incidence of mortality and signs of local and systemic toxicity during the study and then were sacrificed and subjected to a complete necropsy. Additional concurrent recovery groups of three rabbits of each sex at vehicle control and high dose level were treated similarly but, after cessation of treatment period were further observed for reversal of toxicity and delayed toxicity, if any, for a period of 14 days.

Assessment of potential systemic and local toxicity was carried out by evaluating all crucial and necessary parameters. Lupin's LUBT010 at and up to the dose of 1.5 mg per eye, and Lucentis at the dose of 0.5 mg per eye did not cause any deaths among the treated rabbits. They did not induce any abnormal clinical signs in rabbits of either sex, during the period of treatment and the 14-day recovery period.

Ophthalmoscopic examinations made on all rabbits prior to and weekly after commencement of the treatment did not reveal incidence of any significant or adverse ophthalmic findings. A few instances of minimal and unilateral opacities haziness developed either in aqueous humour, lens or the vitreous cavity were not dose dependent, and were reversible in nature. These findings were ascribed to the procedure of mechanical trauma caused during the process of making IVT injections (iatrogenic).

Values of the intra-ocular pressure (IOP) of all treated rabbits from the study, as determined before making each IVT injection on days 1, 15 and 29, and at end of the 14-day recovery period, were found to vary between 20.7 mmHg to 22.8 mmHg, and did not differ significantly from those of the rabbits from control groups on respective days.

Treatment with either Lupin's LUBT010 or Lucentis over four weeks did not induce any alterations in their growth as apparent from their body weights recorded weekly during the study. The values of group mean daily food consumption per rabbit, in animals treated with Lupin's LUBT010 or Lucentis were found to be comparable to those of the vehicle control group during the treatment period and the 14-day recovery period.

Lupin's LUBT010 at and up to the dose of 1.5 mg per eye, and Lucentis at the dose of 0.5 mg per eye, did not induce any remarkable and adverse changes with respect to the values of haemoglobin,

haematocrit (PCV), erythrocyte indices (mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), total and differential white cell (WBC) counts, reticulocyte counts, platelet counts, coagulation parameters (prothrombin time and activated partial thromboplastin time) and in the morphology of blood cells of the treated rabbits, as evident from microscopic examination of stained blood smears.

Lupin's LUBT010 at and up to the dose of 1.5 mg per eye and Lucentis at the dose of 0.5 mg per eye, did not induce any alterations in their clinical chemistry parameters as apparent from their plasma levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, bilirubin (total), albumin, protein (total), globulin (calculated), glucose, cholesterol (total, low-density lipoprotein (LDL), cholesterol, high-density lipoprotein (HDL), triglycerides, creatinine, urea nitrogen, calcium, phosphorus, potassium, sodium, and albumin/globulin (A/G) ratio. Treatment of male and female rabbits with Lupin's LUBT010 and Lucentis did not alter any of their urinalysis parameters when examined at end of the treatment period.

Ranibizumab did not adversely affect the immune system of male and female rabbits in this study. The assessment of the immunotoxic potential of ranibizumab was based upon the observations on the primary indicators of immune toxicity, derived from routine measurements and examinations performed during toxicity studies such as haematology and serum chemistry profiles, routine histopathology examinations of the lymphoid tissues, (e.g. spleen, lymph nodes, thymus, gut-associated lymphoid tissue [GALT], in particular Peyer's patches), and bone marrow, and non-lymphoid tissues such as kidney and liver.

4.4.3. Genotoxicity

No dedicated genotoxicity studies were conducted in accordance with the "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*" (EMA/CHMP/BMWP/403543/2010).

4.4.4. Carcinogenicity

No dedicated carcinogenicity studies were conducted in accordance with the "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*" (EMA/CHMP/BMWP/403543/2010).

4.4.5. Developmental and reproductive toxicity

No dedicated reproductive and developmental toxicity studies were conducted in accordance with the "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*" (EMA/CHMP/BMWP/403543/2010).

4.4.6. Toxicokinetics and exposure margins

Not applicable.

4.4.7. Local tolerance

Examination of the local/ocular tolerance was integrated into the repeat-dose toxicity study (RDTS) summarised in section 4.4.2 of this assessment report.

Gross external examinations of the sites of injections i.e. the eyes, during necropsy, also did not reveal any gross abnormalities in male and female rabbits treated with ranibizumab. The histopathological examinations conducted on both eyes of each of the rabbits from all groups of this study, including the vehicle control group, the Lucentis treated group and the recovery groups, did not reveal any remarkable and adverse alterations which could be ascribed to exposure to ranibizumab at and up to the dose level of 1.5 mg/eye. The test article LUBT010 and the reference article Lucentis did not differ from each other with respect to their local tolerance in the eyes of rabbits when administered by IVT injections.

4.4.8. Other toxicity studies

Not applicable.

4.4.9. Ecotoxicity/environmental risk assessment

Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits biologic activity if human VEGF-A.

There is no evidence of any pharmacological effects of ranibizumab outside the body. The dose of ranibizumab given to an individual patient by IVT injection is 0.5 mg through IVT route of administration and identical to that given for the Lucentis, which is already an approved product.

Significant elimination of intact LUBT010 from humans is unlikely because protein chains are metabolized to produce amino acids that are filtered by the kidney and normally reabsorbed. If any LUBT010 was eliminated intact, significant biodegradation to amino acids would occur in waste treatment facilities. On the rare chance that LUBT010 survives in the environment, exposure of susceptible aquatic organisms by absorption of LUBT010 is very unlikely.

LUBT010 is a recombinant human protein that consists entirely of naturally occurring molecular amino acids; thus, the metabolism of LUBT010 would not create novel chemical entities. Outside of the human body, LUBT010 metabolites would enter a vastly large pool of molecular precursors for recycling within the environment.

For Ranibizumab, the environmental risk assessment (ERA) consists of a justification for not submitting ERA studies. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Ranibizumab is not expected to pose a risk to the environment.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

The preclinical study of Lupin's biosimilar Ranibizumab (LUBT010) is adequate, comprehensive and thorough in support of a biosimilar development.

Pharmacodynamic: as per the consolidated outcome of VEGF-A165 ELISA and SPR analyses with the different VEGF-A isoforms including VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A145, VEGF-A189, and VEGF-A206, similarity was established between Lucentis EU and LUBT010 with respect to biological activity, ligand binding and binding kinetics.

Although some differences were observed for two LUBT010 batches (in the study "Potency by VEGF-

A121 Enzyme Fragment Complementation (EFC) Assay using HEK293-KDR/KDR cells"), this is likely due to inherent method variations and is specific to this assay. However, the same LUBT010 batches complied with the two-sided QR when analysed with an orthogonal functional assay for VEGF-A121 binding (binding kinetics by SPR).

Joint results of HUVEC anti-proliferation assays and EFC assays for VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A145, and VEGF-A189, similarity was established between Lucentis EU and LUBT010 with respect to biological activity and potency.

Secondary pharmacology, safety pharmacology and pharmacodynamic drug interactions were not investigated for LUBT010 solution for injection 10 mg/mL, which is acceptable according to the applicable guideline(s).

Overall, the submitted pharmacodynamic (PD) studies adequately support the proposed indication.

Toxicology: no single dose toxicity studies were performed with LUBT010, which is acceptable.

The applicant conducted a preclinical toxicity study of LUBT010 in the rabbit. The rabbit as an animal model is accepted, as it is a common species used for ocular toxicity testing. Treatment with Lupin's LUBT010 at and up to the dose of 1.5 mg/eye and Lucentis at the dose of 0.5 mg per eye, did not cause remarkable adverse effects on the group mean absolute and relative values of weights of liver, kidneys, adrenals, testes / uterus, brain, lungs, spleen and heart of the rabbits.

The necropsy examination of all rabbits conducted at termination of the study, and the microscopic examination of all tissues /organs of all control group rabbits and all rabbits treated at high dose level of 1.5 mg/eye of the test article, did not reveal any incidence of ranibizumab related alterations, suggestive of absence of any systemic effects of the treatment.

No systemic and/or adverse effects were found at the gross examinations. The histopathological examinations in regard of the local tolerance at the injection sites, was conducted on both eyes of each of the rabbits from all groups of the study, including the vehicle control group, the Lucentis treated group and the recovery groups, did not reveal any remarkable and adverse alterations which could be ascribed to exposure to ranibizumab at and up to the dose level of 1.5 mg/ eye. The test article Lupin's LUBT010 and the reference article Lucentis® did not differ from each other with respect to their local tolerance in the eyes of rabbits when administered by IVT injections.

Considering the results of this study in which rabbits received IVT injections of Lupin's LUBT010 manufactured by Lupin at dose levels of 0.5 mg, 1.0 mg or 1.5 mg per eye in 50 microlitre volumes every two weeks over a four week period (on days 1, 15 and 29), it can be concluded that LUBT010 manufactured by Lupin did not induce any systemic effects, adverse or otherwise, in rabbits treated and up to the dose level of 1.5 mg per eye, i.e. 3.0 mg/rabbit. With respect to its systemic effects, the no observed adverse effect level (NOAEL) of LUBT010 of Lupin in rabbit was found to be greater than 3.0 mg/rabbit. LUBT010 of Lupin was well tolerated in the eyes of rabbits following its IVT injections and its local tolerance at injection sites was found to be comparable to the reference product Lucentis. In regard of the local/ocular effects, the NOAEL of LUBT010 of Lupin in rabbit was found to be greater than 1.5 mg/eye.

Of note: although this study has not demonstrated any meaningful differences between LUBT010 and Novartis Lucentis, the Lucentis used for this *in vivo* study was marketed in India and can't, as such, be regarded in support of the biosimilarity approach between LUBT010 and EU-Lucentis.

No dedicated genotoxicity studies, no carcinogenicity studies, no developmental and reproductive toxicity studies, nor any other toxicity studies were conducted, in accordance with the "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*"

(EMA/CHMP/BMWP/403543/2010).

ERA: The applicant provided a justification for not conducting environmental toxicity studies with LUBT010. An expert assessment without technical dossier (study reports) was handed in, legitimately justifying the absence of an ERA for the MAA of LUBT010.

Based on the molecular characteristics of LUBT010, in alignment with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2) that states "... amino acids, peptides, proteins …are unlikely to result in significant risk to the environment", and to the best knowledge of the Environmental Assessment Expert, no environmental hazard exists for LUBT010.

The comparative quality and non-clinical *in vitro* assessment of Lupin drug product (DP) did not identify any significant concerns in relation to biosimilarity to the reference product and, as the *in vitro* assays may be more specific and sensitive than studies in animals, the results of the *in vivo* study were not considered necessary from a non-clinical perspective to support the MAA, in accordance with the applicable EMA Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

4.5.2. Conclusions

The results of the preclinical program for Lupin's LUBT010 demonstrated a comparable profile between LUBT010 and EU sourced Lucentis in the provided studies, supporting the MAA.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP, as claimed by the applicant.

The applicant provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

For the clinical trial LRP/LUBT010/2016/008 a request for a routine GCP inspection was adopted and conducted for the following reasons: no inspections, sponsor never inspected, single trial, most data obtained in non-EU countries. The routine GCP inspection was adopted in line with the guideline "*Points to consider for assessors, inspectors, and EMA inspection coordinators on the identification of triggers for the selection of applications for 'routine' and/or 'for cause' inspections, their investigation, and scope of such inspections*". The integrated inspection report (EMA/IN/0000263152, 2025) was provided and outcomes, as well as recommendations, were considered for this MAA. One site-specific critical finding and several major findings at the inspected sites and the sponsor's site(s) were identified, which are further described in section 2.4.3 of this assessment report.

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier (see section 2.4.3).

5.1.2. Tabular overview of clinical trials

Table 4: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1					
LRP/LUBT010/2022/001	RD, OL study 3-month treatment period, EOS at Day 84	Lupin ranibizumab (LUBT010) 0.5 mg Q4W IVT or Lucentis 0.5 mg Q4W IVT	Adults aged ≥ 50 years yrs with nAMD	PK, safety, immunogenicity, PD. Primary endpoint: Cmax after first dose (descriptive)	20 randomised and treated LUBT010 IVT Q4W: 10/10 Lucentis IVT Q4W: 10/10
Phase 3					
LRP/LUBT010/2016/008	RD, DB study 12-month treatment period, EOS at Day 360	Lupin ranibizumab (LUBT010) 0.5 mg Q4W IVT or Lucentis 0.5 mg Q4W IVT	Adults aged ≥ 50 years yrs with nAMD	efficacy, safety, and immunogenicity Primary endpoint: Difference in mean change in BCVA from baseline in the study eye at the end of month 12 between LUBT010 and Lucentis arms.	600 randomised and treated LUBT010 IVT Q4W: 299/299 Lucentis IVT Q4W: 301/301

RD = randomised; DB = double blind; OL =open label; IVT = intravitreal; Q4W = every 4 weeks

5.2. Clinical pharmacology

5.2.1. Methods

The comparative PK of ranibizumab after administration of Lupin ranibizumab (LUBT010) or Lucentis in the comparative PK-PD study in patients with nAMD (study LRP/LUBT010/2022/001) were evaluated by means of ranibizumab determination in human serum samples using an Enzyme-linked immunosorbent assay (ELISA).

The applicant has adopted an electrochemiluminescence (ECL) bridging immunoassay to screen, confirm and quantify anti-drug antibodies against Ranibizumab in human serum, measured by meso scale discovery (MSD) technique. Furthermore, the applicant proposed a method for detection of Neutralizing antibodies against Ranibizumab in human serum using ECL competitive ligand binding assay technique.

All assays were validated at the Bioanalytical Research department Lupin Bioresearch Centre.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

PK only has a modest part in a biosimilar comparison of an ophthalmic product, as the systemic exposure after IVT administration is negligible and mostly variable. However, PK evaluation of systemic exposure can give some reassurance that the exposure levels are within a similar range as for the reference product.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

Not applicable.

5.2.2.2.2. Physiology based pharmacokinetic model

Not applicable.

5.2.2.3. Absorption

Not applicable.

5.2.2.4. Bioequivalence

No PK studies were conducted in healthy volunteers. A comparative PK comparison to demonstrate equivalence between Lupin ranibizumab (LUBT010) and the reference product EU-Lucentis was conducted by means of a stand-alone PK study in the intended indication nAMD (LRP/LUBT010/2022/001). No PK endpoints were included in the pivotal Phase 3 study (LRP/LUBT010/2016/008).

Study LRP/LUBT010/2022/001

Title of Study: A randomised, open label study to compare PK and safety of Lupin ranibizumab with Lucentis in patients with neovascular age-related macular degeneration.

First Patient Enrolled: 06 Oct 2023 (First Patient consented)

Last Patient Completed: 27 Mar 2024 (Last Patient Out)

Study Design

This was a randomised, open label study to compare PK and safety of LUBT010 with Lucentis in patients with nAMD. Approximately 20 patients were planned to be enrolled in this study. Eligible patients were randomly assigned to receive either LUBT010 or Lucentis (in a ratio of 1:1) as a monthly single IVT injection of 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) for 3 months. The study drug was administered at Visit 1 (Day 0), Visit 5 (Day 28 ± 2 day), and Visit 6 (Day 56 ± 2 days).

This study was conducted by 4 Investigators at 4 study centres in India.

Determination of Sample Size

No formal sample size calculation was performed. 20 patients were enrolled in this PK study.

Study population

The patients were selected on the basis of following inclusion and exclusion criteria:

Inclusion Criteria

1. Ambulatory men or women patients with age ≥ 50 years at the time of screening who were capable of understanding and giving written informed consent.
2. Primary or recurrent (anti-VEGF naive) active CNV lesions secondary to AMD. (Active CNV was defined as presence of leakage or intra- or sub-retinal fluid demonstrated by optical coherence tomography (OCT) and confirmed by fluorescein angiography (FA)). (If both eyes were affected and eligible, at Investigator's discretion, only one eye was selected as the study eye).
3. Best corrected visual acuity (BCVA) in the study eye, using Early Treatment Diabetic Retinopathy Study (ETDRS) testing, between 20/40 and 20/320 (Snellen equivalent), both inclusive before pupil dilation.
4. Willingness and ability to undertake all scheduled Visits and assessments.
5. Women, who were of non-childbearing potential (surgically sterile or menopausal), OR, if of childbearing potential using effective birth control and non-pregnant & non-lactating for the duration of the study.

Exclusion Criteria

1. Known hypersensitivity to ranibizumab or any of the components of study medication.

2. Known history of allergy to fluorescein dye.

3. Patients with coexisting CNV lesions secondary to AMD in the non-study eye that would require simultaneous treatment with anti-VEGF therapies during the study period.

4. Scar, fibrosis, or atrophy involving the centre of the fovea in the study eye as assessed by FA.

5. History of vitrectomy, sub-macular surgery, or other surgical intervention for AMD in the study eye.

6. Any other pathology involving the CNV lesion like retrofoveolar atrophy or permanent structural damage to the fovea.

7. Vitreous haemorrhage 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.

8. 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 require IOP-lowering treatment.

9. History of serious complications following surgery in the study eye within 1 year prior to randomization.

10. Previous treatment with intravenous anti-VEGF agents or IVT anti-VEGF agents such as Bevacizumab, Ranibizumab, Aflibercept, Pegaptanib, Brolucizumab in either of the eyes.

11. Previous treatment with IVT steroids (e.g., triamcinolone, anecortave acetate) in the study eye within 3 months prior to randomization.

12. Previous treatment with IVT steroid implant (like Ozurdex®) within 6 months prior to randomization.

13. Concurrent use of systemic anti-VEGF agents.

14. Intraocular surgery (including cataract surgery) in the study eye within 3 months prior to randomization.

15. Concurrent treatment with an investigational drug or device in the non-study eye.

16. 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.

17. Patients who had DME and/or background or proliferative retinopathy were excluded. Likewise, anyone with significant posterior subcapsular cataract were excluded.

18. 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.

19. Active or ongoing ocular infection (e.g., infectious conjunctivitis, keratitis, scleritis, or endophthalmitis) or severe inflammation in either of the eyes.

20. Any concurrent intraocular condition in the study eye that could either require medical or surgical intervention during the study period or conditions that could contribute to a loss (of at least 2 Snellen equivalent lines) of BCVA over the 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 was based on the opinion of the investigator.

21. Any patient with cloudy media from any cause that prevents adequate visualization of the fundus with indirect ophthalmoscopy were excluded.

22. Patients with seropositivity for hepatitis B, hepatitis C, human immunodeficiency virus antibody, or any immunodeficiency and/ or immunosuppressive disease or active systemic infection.

23. 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 electrocardiogram etc.

Randomisation and blinding

The study was an open label randomized study. Twenty eligible patients were enrolled and randomly assigned to one of the possible sequences of LUBT010 and Lucentis in a ratio of 1:1. The order of receiving the LUBT010 and Lucentis for each patient was determined according to randomization schedule. Randomisation was generated using SAS® (SAS Institute Inc., USA) Version 9.4. Once the eligibility of the patient was confirmed, the treatment allocation was done as per randomization schedule by study team for each patient. The randomization was balanced, and the code was kept under controlled access. The study personnel involved in the sample analysis were kept blinded from the randomization code during the entire study.

Description of trial intervention

Table 5: Description of trial intervention

Study drug name	LUBT010	Lucentis®
Product Name	RANIBIZUMAB INJ. 2.3 MG/VIAL (10 MG/ML)	LUCENTIS LIVI 0.5 MG/0.05 ML 1X1 GB (FN)
Dosage form and strength:	Injection in vial 0.05 mL of 10 mg/mL	Injection in vial 0.05 mL of 10 mg/mL
Route of administration	Intravitreal injection	Intravitreal injection
Packaging and labeling:	A single-use, 2-cc glass vial packaged individually in carton	A single-use, 2-cc glass vial packaged individually in carton.
Storage:	2°to 8°C (36°-46°F)	2°to 8°C (36°-46°F)
Source:	Lupin Ltd	NOVARTIS PHARMA STEIN AG Schaffhauserstrasse 4332 STEIN Switzerland

Concomitant and rescue medication

Any other medications/treatments required by the patient that were not expected to interfere with study assessments was allowed on a case-by-case basis and as deemed appropriate by the Investigator. The investigator instructed the patient to notify the study site about any new medications taken after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies administered after the patient was enrolled into the study was recorded in the case report form including start and stop dates and reason for use. Therapies other than anti-VEGF therapy, like thermal laser and verteporfin PDT for AMD were allowed in the non-study eye at the discretion of the Investigator and if the non-study eye can await treatment with Anti-VEGF therapy for the study duration. Supplementation with antioxidant & minerals (non-investigational treatments) (e.g., lutein zeaxanthin or beta carotene, Vitamin C, E, and zinc) was allowed.

Other therapies for the treatment of AMD, including but not limited to verteporfin photodynamic therapy (PDT), pegaptanib, bevacizumab, aflibercept or any other anti-VEGF therapy was not allowed in the study eye during the study. Anti-VEGF therapy was not allowed for non-study eye during the study. Other biologics were not allowed during the study. Any other experimental therapy for treatment of AMD was not allowed during the study. In the light of these restrictions, only those patients with bilateral AMD whose non-study eye awaited the treatment with anti VEGF therapy for the study duration were allowed to participate in the study.

Objectives and endpoints

Primary Objective

The primary objective was to assess the PK of Lupin's ranibizumab as compared to Lucentis.

Primary endpoint: descriptive assessment of peak systemic drug levels (C_{max}) after first dose.

Secondary Objective

The secondary objective was to assess the safety and tolerability of Lupin's ranibizumab as compared to Lucentis and to assess the immunogenicity of Lupin's ranibizumab as compared to Lucentis.

The exploratory objective was to assess the change in central foveal thickness (CFT) with Lupin's ranibizumab as compared to Lucentis.

Secondary endpoints:

- Descriptive assessment of peak systemic drug levels (C_{max}) after third dose.
- Descriptive assessment of trough systemic drug levels (C_{trough}) before second and third dose.
- Proportion of patients with anti-drug antibodies at Day 28, 56, and 84.
- Incidence of treatment emergent adverse events.

Exploratory Endpoint: descriptive assessment of change from baseline in retinal thickness CFT at month 1 and month 3).

Data Quality Assurance

Data handling, including data quality assurance, was conducted according to the regulatory guidelines (e.g., ICH GCP).

PK Analysis

The PK and statistical evaluation were carried out at Lupin Bioresearch Center, India. The PK parameters Ranibizumab were determined by non-compartmental methods using Phoenix Software version 8.3.3 (USA). Analyses of the PK parameters are based upon the PK Analysis Set. The time deviations during sample collection were treated as follows: The pre-dose blood samples were collected within 60 min prior to dosing. The actual blood collection time were recorded in appropriate data sheet. In all such cases actual time of collection were incorporated at the time of data analysis. However, the actual sampling times were used to calculate pharmacokinetic parameters, except for pre-dose samples, which were always reported as zero (0.00), regardless of time deviations.

Analysis Population

- Enrolled Set (ENR) included all patients who provide informed consent for this study.
- Randomised Set (RAN) included all patients who are randomized irrespective of receiving study treatment.
- Immunogenicity Analysis Set (IGS): All patients who receive at least 1 dose of study medication have at least one immunogenicity sample with valid result.
- Safety Analysis Set (SAF): All patients who receive at least 1 dose of study medication
- Pharmacokinetic Analysis Set (PKS): All patients who received at least 1 dose of study medication and had at least one PK sample with valid result.
- Pharmacodynamic analysis set (PDS): all randomised patients with evaluable pharmacodynamic data.

Statistical Analysis

Handling of dropouts or missing data: as per SAP no missing data imputation was done. All concentration values below the limit of quantification (BLQ) were set to zero for all PK and summary

calculations. Any missing samples were reported as 'Missing' and were not included for PK and summary calculations.

Analysis of the primary PK endpoint was based on PKS. The primary endpoint of the study was the descriptive assessment of systemic drug levels measured at 24 to 168 hours (close to C_{max}) after first study dose. The summary statistics included number of patients, arithmetic mean, geometric mean, standard deviation, minimum, median, maximum, and coefficient of variation (%CV) for C_{max} was calculated and reported.

Analysis of the secondary endpoint was based on PKS. The secondary endpoint of the study was the descriptive assessment of systemic drug levels measured at 24 to 168 hours (close to C_{max}) after third dose and descriptive assessment of trough systemic drug levels (C_{trough}) before second and third dose. The summary statistics included number of patients, arithmetic mean, geometric mean, standard deviation, minimum, median, maximum, and %CV for C_{max} and C_{trough}.

The exploratory/PD endpoint of CFT was descriptively assessed as the percentage change from baseline in retinal thickness (CFT at screening and Day 84). Summary of actual value, change from baseline and percentage change from baseline by treatment arm and Visit for CFT was provided for SAF. A by-patient listing of CFT for all Visits was provided for SAF.

The immunogenicity analyses were performed using the IGS. The number and percentage of patients with positive results for binding antibodies to ranibizumab and with positive neutralizing antibodies to ranibizumab were presented by treatment arms in each visit (i.e., Day 1, Day 28, Day 56 and Day 84).

The results were presented for treatment emergent binding anti-drug-antibodies (ADA) and neutralising antibodies (NAb) incidence. Treatment emergent ADA was defined as patients with treatment induced ADA (positive post-baseline ADA with a negative or no result at baseline for ADA) or treatment boosted ADA (ADA titer was at least 9-fold from the baseline titer at any time after the initiation of drug administration, in a patient who had a pre-existing ADA at baseline).

Treatment emergent NAb was defined as patients with treatment induced Nab (positive post-baseline NAb with a negative or no result at baseline for NAb).

In addition, the overall incidence of treatment emergent ADAs and NAb up to Month 3 (End of Study) visit was summarised.

For calculation of the overall incidence of ADA, patients with at least one positive treatment emergent ADA response up to the relevant time point was considered as positive. Patients with positive result at multiple time points were counted only once. For calculation of overall incidence of NAb, patients with at least one positive treatment emergent NAb response up to the relevant time points were considered as positive.

In the SAF population (202 patients randomised; 100%) treatment was assigned based upon the treatment patients actually received regardless of the treatment to which they were randomised. The Safety Analysis Set was used for all analyses of safety data.

Results

Participants flow and numbers analysed

In the study, 23 subjects were screened and 20 were enrolled. All patients completed the study and no discontinuations were reported. Consequently, the ENR, RAN, IGS, PKS and PDS sets were all identical and included 10 subjects per arm.

Protocol Deviations

Protocol deviations were reported in 11 patients (55.0%), including 5 patients (50.0%) in the LUBT010 arm and 6 patients (60.0%) in the Lucentis arm. The most frequently reported deviations were related to visit schedule (55.0%) and study procedures (45.0%). These deviations were not considered to have impacted the pharmacodynamic evaluation.

Baseline Data

Table: Demographic characteristics (RAN)

Characteristic	Statistic	LUBT010 (N = 10)	Lucentis (N = 10)	Total (N = 20)
Age (years)	N	10	10	20
	Mean (SD)	62.3 (9.0)	67.1 (6.9)	64.7 (8.2)
	Median	64	68	65
	Min – Max	50 - 76	56 - 76	50 - 76
Gender				
Male	n (%)	5 (50.0)	6 (60.0)	11 (55.0)
Female	n (%)	5 (50.0)	4 (40.0)	9 (45.0)
Race				
Asian	n (%)	10 (100.0)	10 (100.0)	20 (100.0)
Other	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Hispanic or Latino	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	n (%)	10 (100.0)	10 (100.0)	20 (100.0)
Not Reported	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Weight(kg)	n	10	10	20
	Mean (SD)	63.860 (10.689)	61.945 (13.055)	62.903 (11.654)
	Median	65.63	60.50	63.60
	Min - Max	49.95 - 82.00	43.50 - 83.75	43.50 - 83.75

Source Table: 14.1.3.1.1, Listing 16.2.4.1
Max = Maximum, Min = Minimum, SD = Standard Deviation
N is the number of patients in the randomized set. n is the number of patients in each category. Percentages are calculated based o n .

Medical history and concurrent illness

At least one medical or surgical history was reported for 17 (85.0%) patients. The most commonly reported conditions by System Organ Class (SOC) were Vascular disorders and Eye disorders.

The Medical history reported (by preferred term (PT)) were:

- Hypertension: 10 (50.0%) patients overall, including 3 (30.0%) patients in LUBT010 arm and 7 (70.0%) patients in Lucentis arm.
- Cataract operation: 5 (25.0%) patients overall, including 1 (10.0%) patient in LUBT010 arm and 4 (40.0%) patients in Lucentis arm.
- Prior and Concomitant Medications

All 20 randomised patients had at least 1 prior and concomitant medication, respectively. In line with the reported medical and procedural history, most commonly administered prior medications were fluorescein 19 (95.0%) followed by proxymetacaine 13 (65.0%) and phenylephrine tropicamide 12 (60.0%). Most commonly administered concomitant medications were povidone-iodine and

proxymetacaine each by 20 (100.0%) patients followed by moxifloxacin used by 18 (90.0%) patients and fluorescein used by 14 (70.0%) patients. None of the randomised patients were administered prohibited medication in the study.

Outcomes

PK Endpoints

The PK profiles of LUBT010 and Lucentis were descriptively evaluated in patients with neovascular AMD. Analyses included serum concentration measured up to 168 hours after first and third dose [close to maximum serum concentration (C_{max})]; and the trough serum concentration (C_{trough}) before second and third dose.

Table 6: Summary of Ranibizumab PK parameters (PKS)

Parameter	Statistic	LUBT010 (N=10)	LUCENTIS (N=10)
C_{max} (ng/mL) after Dose 1	Mean (SD) Median Min, Max CV% Geometric mean	8.5001 (10.1016) 3.881 0.904, 32.520 118.84 4.8350	10.9116 (14.8635) 4.855 1.922, 49.232 136.22 6.1781
C_{max} (ng/mL) after Dose 3	Mean (SD) Median Min, Max CV% Geometric mean	4.3224 (3.6020) 3.681 0.000, 12.260 83.33 NE	6.7416 (5.4706) 4.973 3.268, 21.456 81.15 5.6023
C_{trough} (ng/mL) before Dose 2	Mean (SD) Median Min, Max CV% Geometric mean	0.0000 (0.0000) 0.0000 0.0000, 0.0000 NE NE	0.0000 (0.0000) 0.0000 0.0000, 0.0000 NE NE
C_{trough} (ng/mL) before Dose 3	Mean (SD) Median Min, Max CV% Geometric mean	0.0000 (0.0000) 0.0000 0.0000, 0.0000 NE NE	0.0000 (0.0000) 0.0000 0.0000, 0.0000 NE NE

C_{max} = peak serum concentration; C_{trough} = concentration reached by a drug immediately before the next dose is administered; CV% = percentage coefficient of variation; Max = maximum; Min = minimum; N = number of subjects; NE = non-estimable; PK = pharmacokinetic; SD = standard deviation

For the calculation of PK parameters, concentration values that are below the limit of quantitation are treated as zero (0).

Descriptive PK Analysis

Table 7: Ranibizumab concentrations (ng/mL) following the administration of study treatment (PKS)

		Dose 1					Dose 2	Dose 3					
Treatment	Patient	Day 0 (Pre-dose)	Day 0 (Post-dose)	Day 1	Day 3	Day 7	Day 28 (Pre-dose)	Day 56 (Pre-dose)	Day 56 (Post-dose)	Day 57	Day 59	Day 63	Day 84
Lucentis	21-001	0.000	23.328	7.957	3.308	2.557	0.000	0.000	3.399	3.342	2.198	1.602	0.000
LUBT010	21-002	0.000	10.840	7.111	3.512	2.418	0.000	0.000	3.139	3.301	2.735	2.372	0.000
LUBT010	21-003	0.000	19.288	4.355	1.932	1.370	0.000	0.000	12.260	2.599	1.318	0.000	0.000
LUBT010	21-004	0.000	32.520	5.110	3.373	1.782	0.000	0.000	6.949	2.954	2.038	1.301	0.000
Lucentis	21-005	0.000	4.597	4.172	3.188	1.917	0.000	0.000	8.749	3.522	2.817	1.456	0.000
Lucentis	21-006	0.000	3.351	5.112	3.379	1.692	0.000	0.000	1.060	7.185	4.128	1.521	0.000
Lucentis	21-007	0.000	9.601	5.074	3.103	2.268	0.000	0.000	5.430	4.783	3.716	2.195	0.000
Lucentis	22-001	0.000	6.285	3.883	2.100	1.125	0.000	0.000	1.463	3.586	3.344	0.000	0.000
Lucentis	22-002	0.000	2.694	3.857	3.402	2.171	0.000	0.000	5.926	4.315	2.835	2.373	0.000
LUBT010	22-003	0.000	0.000	0.000	0.000	0.904	0.000	0.000	NRV	4.151	2.574	2.078	0.000
LUBT010	22-004	0.000	0.000	0.000	1.696	0.987	0.000	0.000	NRV	0.889	2.684	1.506	0.000
Lucentis	22-005	0.000	49.232	4.791	3.398	2.072	0.000	0.000	21.456	3.536	3.130	1.461	0.000
LUBT010	23-001	0.000	2.299	3.166	2.836	0.000	0.000	0.000	0.000	1.509	0.000	0.000	0.000
LUBT010	23-002	0.000	2.369	3.096	2.986	1.608	0.000	0.000	0.000	0.000	0.000	0.000	0.000
LUBT010	24-001	0.000	6.665	3.994	4.713	2.176	0.000	0.000	3.615	2.926	4.060	2.338	0.000
Lucentis	24-002	0.000	1.212	2.650	1.554	0.978	0.000	0.000	2.372	3.902	1.235	1.035	0.000
LUBT010	24-003	0.000	2.231	2.192	1.943	1.139	0.000	0.000	1.293	1.055	0.943	0.000	0.000
Lucentis	24-004	0.000	1.038	1.922	1.503	0.918	0.000	0.000	2.165	2.455	3.268	1.383	0.000
Lucentis	24-005	0.000	2.532	2.000	1.129	1.052	0.000	0.000	0.000	4.515	1.425	1.382	0.000
LUBT010	24-007	0.000	3.685	4.595	1.868	1.113	0.000	0.000	7.017	5.332	1.229	1.202	0.000

NRV= Non reported value

Exploratory Endpoint Assessment

Assessment of Change from Baseline in Retinal Thickness (Central Foveal Thickness)

CFT was measured by OCT at baseline, and at the end of month 1 and month 3.

Table 8: Mean change in the retinal thickness from baseline in the study eye at the end of 1 and 3 months (SAF)

Visit	Treatment	Mean	SD	Min	Median	Max	Mean (SE)	95% CI	P-Value
Baseline	LUBT010 (N=10)	428.1	154.2	291	379	770			
	Lucentis (N=10)	366.1	86.3	288	339	553			
Month 1 Actual	LUBT010 (N=09)	372.2	195.8	232	310	873			
	Lucentis (N=10)	289.1	102.7	165	272	553			
Change from Baseline	LUBT010 (N=09)	-71.1	132.7	-343	-66	103		(-192.77, 50.55)	
	Lucentis (N=10)	-77.0	77.8	-220	-59	29		(-143.07, -10.93)	
Percent Change from Baseline	LUBT010 (N=09)	-15.8	25.6	-54	-18	32		(-39.19, 7.69)	
	Lucentis (N=10)	-20.5	19.4	-57	-18	10		(-37.02, -4.07)	
	Difference (LUBT010-Lucentis)						4.8 (10.5)	(-17.60, 27.18)	0.655

Table 9: Mean change in the retinal thickness from baseline in the study eye at the end of 1 and 3 months (SAF) cont'd

Month 3 Actual	LUBT010 (N=10)	337.0	193.6	191	304	863			
	Lucentis (N=10)	265.5	44.0	210	252	344			
Change from Baseline	LUBT010 (N=10)	-91.1	135.9	-397	-57	93		(-206.53, 24.33)	
	Lucentis (N=10)	-101	107.0	-298	-92	33		(-191.49, -9.71)	
Percent Change from Baseline	LUBT010 (N=10)	-21.2	24.2	-62	-17	12		(-41.74, -0.66)	
	Lucentis (N=10)	-23.8	22.5	-54	-27	11		(-42.88, -4.67)	
	Difference (LUBT010-Lucentis)						2.6 (10.4)	(-19.38, 24.54)	0.808

Baseline is defined as the last valid assessment performed prior to administration of the first dose of study treatment

Change in BCVA from baseline in the study eye

The Mean (SD) change in BCVA from baseline in the study eye was assessed at the screening visit, at baseline and at visit 5, visit 6 and EOS/ or early discontinuation.

Table 10: Mean change in BCVA from baseline in the study eye at the end of 1 and 3 months (SAF)

Visit	Statistic	LUBT010 (N = 10)		Lucentis (N = 10)	
		Actual Values	Change from Baseline	Actual Values	Change from Baseline
Baseline	N	10		10	
	Mean (SD)	40.0 (9.1)		50.8 (11.5)	
	SE	2.9		3.6	
	Median	38		56	
	Min, Max	25, 55		25, 62	
Month 1	N	10	10	10	10
	Mean (SD)	48.0 (13.5)	8.0 (7.1)	55.3 (13.3)	4.5 (5.4)
	SE	4.3	2.2	4.2	1.7
	Median	47	5	58	3
	Min, Max	25, 70	0, 25	25, 75	-1, 15
Month 3	N	10	10	10	10
	Mean (SD)	50.7 (10.0)	10.7 (3.4)	57.9 (14.0)	7.1 (6.1)
	SE	3.2	1.1	4.4	1.9
	Median	50	10	60	7
	Min, Max	35, 67	5, 15	25, 75	0, 17

N is the number of patients in the full analysis set.
Baseline is defined as the last valid assessment performed prior to administration of the first dose of study treatment
Source Table: 14.6.1.2

5.2.2.5. Distribution

Not applicable.

5.2.2.6. Metabolism

Not applicable.

5.2.2.7. Elimination

Not applicable.

5.2.2.8. Dose proportionality and time dependency

Not applicable.

5.2.2.9. Pharmacokinetics in the target population

Please refer to section 5.2.2.4 *Bioequivalence* (Study LRP/LUBT010/2022/001) for comments on PK data in patients with nAMD.

5.2.2.10. Special populations

No new data were collected on PK in special populations. All provided information was based on historical data for Lucentis. Thus, no formal studies were conducted to examine the PK of Lupin ranibizumab in patients with renal/hepatic impairment. This is reflected accordingly in the product information (PI).

No specific PK studies were performed to investigating the effect of race, gender and weight on the PK of ranibizumab. However, race, gender and weight are unlikely to have an effect on the systemic exposure of this ophthalmic applied product. Additionally, no investigation has been provided to explore the potential impact of age on the systemic exposure of ranibizumab after IVT injection since this is not required for a biosimilar application.

5.2.2.11. Pharmacokinetic interaction studies

Not applicable.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human VEGF-A. It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the nAMD, pathologic myopia and choroidal neovascularization (CNV) or to visual impairment caused by either DME or macular oedema secondary to RVO in adults.

5.2.3.2. Primary and secondary pharmacology

No clinical comparative PD studies have been performed with LUBT010. No accepted specific PD markers exist, being predictive of efficacy/safety of ranibizumab in patients.

PD similarity of LUBT010 and Lucentis in terms of VEGF inhibition has been investigated as part of the biosimilarity exercise at the quality/non-clinical level.

At the clinical level, retinal thickness (e.g., central retinal thickness [CRT]), which well addresses the PD aspects of ranibizumab, was assessed by OCT. Results are discussed in section 5.2.2.4. Bioequivalence.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Not applicable.

5.2.3.4. Genetic differences in PD response

Not applicable.

5.2.3.5. Immunological events

Study LRP/LUBT010/2022/001

The study design is presented in section 5.2.2.4. Bioequivalence.

Blood sampling for immunogenicity was collected at Day 0 (pre-dose), Month 1/Day 28 ± 2 days (pre-dose), Month 2/Day 56 ± 2 days (pre-dose), Month 3/Day 84 ± 2 days coinciding with PK sample.

At days 0, 28 and 56, 4 subjects per arm showed ADA +. At day 84, 2 subjects in the LUB010 arm and 3 subjects in the Lucentis arm were ADA positive.

Treatment-emergent ADA was defined as patients with treatment-induced ADA (positive post baseline ADA with a negative or no result at baseline for ADA) or treatment-boosted ADA (ADA titer was at least 9-fold of the baseline titer at any time after the initiation of drug administration, in a patient who had a pre-existing ADA at baseline). At day 28, 1 subject per arm was considered to have treatment emergent ADA. At day 56 and 84, 1 subject in the LUB010 arm and 2 subjects in the Lucentis arm were considered to have treatment emergent ADA.

None of the ADA were Nab.

Study LRP/LUBT010/2016/008

The study design is presented in section 6.3.2 of Clinical Efficacy.

Blood samples for immunogenicity were collected before study drug dose (predose) on Day 1, Day 31, Day 91, Day 181, Day 271, and at EOS visit (Day 360).

The number and percentage of patients with positive result for ADA as well as NAb to ranibizumab are presented separately, by treatment arm at each visit. The result was also presented for treatment-emergent ADA and NAb incidence.

Treatment-emergent ADA was defined mentioned before. In addition, overall incidence of treatment-emergent ADA and NAb up to Month 12 (EOS) visit was summarized. Treatment-emergent NAb was defined as patients with treatment-induced NAb (positive postbaseline NAb with a negative or no result at baseline for NAb).

A total of 600 patients were randomized in the study. Of all randomized patients, 590 (98.3%) were included in the IGS) A total of 10 patients were excluded from the IGS, including 6 patients in the LUBT010 and 4 patients from the Lucentis arm. These patients were excluded due to lack of post-baseline data available for ADA and NAb.

Results

Table 11: Summary of ADA and NAb (IGS)

Visit	Parameter	Result	LUBT010 (N=293) n/m (%)	Lucentis (N=297) n/m (%)	Total (N=590) n/m (%)
Baseline	ADA	Positive	25/292 (8.6)	30/295 (10.2)	55/587 (9.4)
		Negative	267/292 (91.4)	265/295 (89.8)	532/587 (90.6)
	NAb	Positive	2/ 25 (8.0)	2/ 30 (6.7)	4/ 55 (7.3)
		Negative	23/ 25 (92.0)	28/ 30 (93.3)	51/ 55 (92.7)
Month 1	ADA	Positive	23/289 (8.0)	25/290 (8.6)	48/579 (8.3)
		Negative	266/289 (92.0)	265/290 (91.4)	531/579 (91.7)
	NAb	Positive	1/ 23 (4.3)	1/ 25 (4.0)	2/ 48 (4.2)
		Negative	22/ 23 (95.7)	24/ 25 (96.0)	46/ 48 (95.8)
Month 3	ADA	Positive	28/277 (10.1)	28/284 (9.9)	56/561 (10.0)
		Negative	249/277 (89.9)	256/284 (90.1)	505/561 (90.0)
	NAb	Positive	1/ 28 (3.6)	1/ 28 (3.6)	2/ 56 (3.6)
		Negative	27/ 28 (96.4)	27/ 28 (96.4)	54/ 56 (96.4)
Month 6	ADA	Positive	36/271 (13.3)	33/271 (12.2)	69/542 (12.7)
		Negative	235/271 (86.7)	238/271 (87.8)	473/542 (87.3)
	NAb	Positive	0/ 36	1/ 33 (3.0)	1/ 69 (1.4)
		Negative	36/ 36 (100.0)	32/ 33 (97.0)	68/ 69 (98.6)
Month 9	ADA	Positive	36/252 (14.3)	31/264 (11.7)	67/516 (13.0)
		Negative	216/252 (85.7)	233/264 (88.3)	449/516 (87.0)
	NAb	Positive	1/ 36 (2.8)	3/ 31 (9.7)	4/ 67 (6.0)
		Negative	35/ 36 (97.2)	28/ 31 (90.3)	63/ 67 (94.0)
Month 12	ADA	Positive	29/253 (11.5)	30/269 (11.2)	59/522 (11.3)
		Negative	224/253 (88.5)	239/269 (88.8)	463/522 (88.7)
	NAb	Positive	4/ 29 (13.8)	3/ 30 (10.0)	7/ 59 (11.9)
		Negative	25/ 29 (86.2)	27/ 30 (90.0)	52/ 59 (88.1)

ADA: Anti-drug Antibody, NAb: Neutralizing Antibody.
N is the number of patients in the Immunogenicity analysis set. m is the number of patients with sample collected at specific visit for ADA and the number of patients with positive ADA at specific visit for NAb. n is the number of patients in each category. Percentages are calculated based on m.
ADA Confirmatory results collected as N/A are reported under Negative category.

Table 12: Summary of incidence of treatment emergent ADA and NAb by visit (IGS)

Visit	Parameter	Result	LUBT010 (N=293) n/m (%)	Lucentis (N=297) n/m (%)	Total (N=590) n/m (%)
Month 1	ADA	Positive	10/289 (3.5)	11/290 (3.8)	21/579 (3.6)
	NAb	Positive	0/ 10	0/ 11	0/ 21
Month 3	ADA	Positive	18/277 (6.5)	15/284 (5.3)	33/561 (5.9)
	NAb	Positive	1/ 18 (5.6)	1/ 15 (6.7)	2/ 33 (6.1)
Month 6	ADA	Positive	24/271 (8.9)	22/271 (8.1)	46/542 (8.5)
	NAb	Positive	0/ 24	0/ 22	0/ 46
Month 9	ADA	Positive	26/252 (10.3)	21/264 (8.0)	47/516 (9.1)
	NAb	Positive	1/ 26 (3.8)	2/ 21 (9.5)	3/ 47 (6.4)
Month 12	ADA	Positive	19/253 (7.5)	21/269 (7.8)	40/522 (7.7)
	NAb	Positive	4/ 19 (21.1)	2/ 21 (9.5)	6/ 40 (15.0)

ADA: Anti-drug Antibody, NAb: Neutralizing Antibody.
N is the number of patients in the Immunogenicity analysis set. m is the number of patients with sample collected at specific visit for ADA and the number of patients with positive treatment emergent ADA at specific visit for NAb. n is the number of patients in each category. Percentages are calculated based on m.
Treatment emergent ADA is defined as patients with treatment induced ADA (positive post-baseline ADA with a negative or no result at baseline for ADA) or treatment boosted ADA (ADA titer is at least 9-fold the baseline titer at any time after the initiation of drug administration, in a patient who had a pre-existing ADA at baseline).
Treatment emergent NAb is defined as patients with treatment induced NAb (positive post-baseline NAb with a negative or no result at baseline for NAb)

Table 13: Summary of overall incidence of treatment emergent ADAs and NAbs up to month 12 (immunogenicity analysis set)

Visit	Parameter	Result	LUBT010 (N=293) n (%)	Lucentis (N=297) n (%)	Total (N=590) n (%)
Month 1	ADA	Positive	10 (3.4)	11 (3.7)	21 (3.6)
	NAb	Positive	0	0	0
Month 3	ADA	Positive	24 (8.2)	21 (7.1)	45 (7.6)
	NAb	Positive	1 (0.3)	1 (0.3)	2 (0.3)
Month 6	ADA	Positive	38 (13.0)	34 (11.4)	72 (12.2)
	NAb	Positive	1 (0.3)	1 (0.3)	2 (0.3)
Month 9	ADA	Positive	46 (15.7)	44 (14.8)	90 (15.3)
	NAb	Positive	2 (0.7)	3 (1.0)	5 (0.8)
Month 12	ADA	Positive	49 (16.7)	53 (17.8)	102 (17.3)
	NAb	Positive	5 (1.7)	4 (1.3)	9 (1.5)

ADA: Anti-drug Antibody, NAb: Neutralizing Antibody.
N is the number of patients in the Immunogenicity Analysis Set. n is the number of patients in each category. Percentages are calculated based on N.
Treatment emergent ADA is defined as patients with treatment induced ADA (positive post-baseline ADA with a negative or no result at baseline for ADA) or treatment boosted ADA (ADA titer is at least 9-fold the baseline titer at any time after the initiation of drug administration, in a patient who had a pre-existing ADA at baseline).
Treatment emergent NAb is defined as patients with treatment induced NAb (positive post-baseline NAb with a negative or no result at baseline for NAb)
For calculation of overall incidence of ADA, patients with at least one positive treatment emergent ADA response up to the relevant timepoint are considered as positive. Patients with positive result at multiple timepoints are counted only once.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Not applicable.

5.2.5. Dose selection and therapeutic window

Not applicable.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The PK profile of the proposed ranibizumab biosimilar Vislyfa (further referred as Lupin ranibizumab, LUBT010) was evaluated with the stand-alone comparative study LRP/LUBT010/2022/001 in the most sensitive indication: nAMD. Ranibizumab is IVT administered directly into the eye. No PK study was conducted in healthy volunteers. Conducting such a study in healthy volunteers is not ethical due to the invasiveness of IVT procedure and not clinically meaningful in the context of biosimilar ranibizumab development. It is therefore acceptable that no separate PK study was conducted in healthy volunteers.

Bioanalytical Methods

The comparative PK of ranibizumab after administration of LUBT010 or Lucentis in the comparative PK-PD study in patients with nAMD (study LRP/LUBT010/2022/001) were evaluated by means of ranibizumab determination in human serum samples using an ELISA. The presented assay for determination of Ranibizumab in human serum was well described and established.

The applicant adopted an ECLIA bridging assay to screen, confirm and quantify antibodies reactive to LUBT010/ Lucentis in human serum matrix. The adopted three-tiered approach for determination of ADAs was well described and developed. The presented method could be considered as valid.

Further, the applicant presented an ECL competitive ligand binding assay for detection of Ranibizumab Nab in human serum. The presented assay was well described and validated.

Study Design of Study LRP/LUBT010/2022/001

Study LRP/LUBT010/2022/001 was a randomized, open-label, parallel group, multicentre, comparative study to evaluate the PK, safety and immunogenicity of LUBT010 compared to the reference product EU-Lucentis. This study also investigated the effect of study drugs on the retinal anatomy marker, central foveal thickness, as an exploratory PD endpoint.

A total of 20 patients from 4 centres in Country 2 were randomized in a 1:1 ratio to receive either LUBT010 [0.5 mg (0.05 mL)] or Lucentis [0.5 mg (0.05 mL)] in the study eye once every 4 weeks for 3 consecutive doses until end of study (EOS) at Day 84. The posology was identical to that of the originator Lucentis, which is endorsed. No stratification was employed to ensure equality between the groups in the clinical trial as regards prognostic factors and the analysis was not adjusted for any prognostic factors. Therefore, differences in baseline characteristics between the two groups should be seen as very critical. Furthermore, it is unclear why it is claimed that the study was open-label while the study personnel involved in the sample analysis were kept blinded to the randomization code throughout the entire study. Therefore, the study was at least assessor-masked, although the treating physician may have known the treatment assignment. This may have influenced treatment decisions, such as treatment discontinuation, rescue medication and assessment of safety events. However, since no prohibited medications were reported and no study discontinuations or treatment discontinuations occurred, the fact that treatment assignment was known to the treating physician does not seem to have influenced the treatment decisions.

Only a very limited number of patients was included in the study (n=10 per study arm), which makes evaluation difficult, as the standard errors for the mean outcomes are exorbitantly large in such small groups. In general, sample size considerations should be based on the expected precision of the effect estimate (width of the confidence interval (CI)) for the comparison of C_{max} between the two treatments if a hypothesis testing is deemed infeasible. However, no justification for the chosen total sample size of 20 patients was provided. Retrospectively justifying the sample size does not seem meaningful. In case of hypothesis testing the sample size usually lies in the remit of the applicant as the sample size influences the power to achieve trial success. The trial success criteria are unclear. However, CHMP agreed on not pursuing this aspect, as this study is only of secondary relevance, and the assessment was mainly based on the pivotal Phase 3 study LRP/LUBT010/2016/008, whereas results of study LRP/LUBT010/2022/001 provided only supportive information.

The applicant received recommendations on the PK analysis as part of the scientific advice procedure (EMEA/H/SA/3346/1/2016/III; 2016), according to which a comparative PK analysis of systemic exposure at baseline and steady state between the reference product and the biosimilar should be present. This should also be correlated with the safety profile of the products and could be obtained from a subset of patients included in the Phase 3 study.

Instead of following the SA, the applicant decided to investigate PK in a stand-alone trial. Generally, it is not critical that PK was not investigated in the pivotal study (LRP/LUBT010/2016/008) but a larger sample size for the PK evaluation could have been achieved in the pivotal study. PK is of minor relevance in a biosimilar comparison of an ophthalmic product, as the systemic exposure after IVT administration is generally negligible and variable. However, PK evaluation of systemic exposure can give some reassurance that the exposure levels are within a similar range as for the reference product.

The eligibility criteria indicate a homogenous study population, similar to those of the Lucentis approval study (MARINA trial) where a population with visual acuity (VA) of 20/40 to 20/320 in the study eye was included. This is acceptable for CHMP. In the pivotal study LRP/LUBT010/2016/008, however, the VA was between 20/40 and 20/200. Hence, results of the supportive and the pivotal studies cannot be compared with each other.

The systemic exposure of LUBT010 and Lucentis was evaluated under repeated doses. The study PK endpoints (C_{max} and C_{trough}) for the systemic exposure after IVT administration are of relevance in a biosimilarity setting and are endorsed.

Blood samples were collected at pre-dose, after first and third IVT injection at 3 hours, 24 hours (close to C_{max}), 72 hours and 168 hours post dosing as well as prior to first, second and third IVT injection to measure systemic concentration of ranibizumab. The chosen time points allow a systemic exposure assessment at both start of treatment and at steady state and are acceptable.

The choice of the secondary endpoints, including the proportion of patients with ADAs and NAbs, the safety endpoints and the exploratory endpoint CFT are generally supported by CHMP.

The definition of the PKS is deemed acceptable as the primary analysis set of the PK endpoint. A formal statistical testing to demonstrate PK similarity between LUBT010 and EU-Lucentis was not performed. It is however agreed that it is not necessary to perform a formal bioequivalence testing due to the low levels of systemic exposure.

The statistical analyses include only descriptive summary statistics, and no missing data imputation was performed. However, a complete case analysis violates the intention-to-treat principle and may lead to bias. Further, intercurrent events (e.g. treatment discontinuation, rescue medication that could influence PK/PD like any other anti-VEGF therapy) could also influence the descriptive PK/PD outcomes. If missing data were not imputed and intercurrent events ignored, the descriptive outcomes would describe the patients who stay in the trial irrespective of them having an intercurrent event. This could bias results to appear more similar than what can be attributable to the pharmacological action.

All patients completed the study, and PK parameters were available from all patients. There were 3 of 480 samples missing (20 patients, 12 sampling points, 2 aliquots) but only in one of two aliquots of the serum samples. None of the randomised patients were administered a prohibited/rescue medication in the study or discontinued the study medication as all patients received 3 injections.

A correlation between PK and the safety results was not investigated, although this was recommended. However, this is generally not possible as only a few (treatment-related) adverse events (AEs) occurred due to the low sample size. Therefore, this was not pursued by CHMP.

Results

A total of 23 patients were screened for the study, 20 of whom met the eligibility criteria. Of these 20, 10 patients each were randomised to the LUBT010 and Lucentis treatment groups. All 20 patients (100.0 %) were enrolled in the RAN, the PKS, the SAF and the IGS and completed the study. In general, the number of patients was balanced by the end of the study. However, as only a limited number of patients was included in the study, it is difficult to draw a conclusion from the study results. Therefore, the results of the study are only used as supportive information.

Eleven (55%) patients reported protocol deviations, all of which were noted as minor deviations. Nine patients had deviations belonging to the group of study procedures where PK samples were taken outside the specified time window. These samples were mostly collected with a delay of 15 minutes. It is assumed that this has no influence on the PK analysis, as the timepoints of blood sampling were far apart (3, 24, 72, 168 hours after treatment) and a balanced number of deviations were reported between the study arms (5 patients in the LUBT010 arm and 4 patients in the Lucentis arm). Six patients did not visit the clinics on the scheduled day (delay of 1-15 days), but dosing and sampling collection were still conducted correctly, and the delays had no impact on the assessments.

The demographics appear balanced in both treatment arms in terms of age, gender, race and weight. No pre-existing conditions were reported to have an impact on treatment with ranibizumab. The study eye

was not treated previously, and this is endorsed by CHMP. The reported prior- and concomitant medications have no influence on the study results. Overall, the study population was balanced between the treatment arms.

Pharmacokinetics

Pre-dose concentrations were not quantifiable in all subjects and post-dose concentrations were generally detectable although being very low. Thus, the drug concentration assay seemed to have generally suitable sensitivity to detect LUBT010 and Lucentis in post-treatment samples.

Figures showing the Mean (±SD) ranibizumab Serum Concentration Time Data showed a similar pattern between study arms over time. The observed variability (CV%) and standard deviation (SD) were high, which confirms the high (and expected) variability of the systemic exposure after IVT administration. The mean (SD) serum C_{max} of ranibizumab after the first dose was 8.5001 (10.1016) ng/mL in the LUBT010 treatment arm and 10.9116 (14.8635) ng/mL in the Lucentis treatment arm. The mean (SD) serum C_{max} of ranibizumab after the third dose was 4.3224 (3.6020) ng/mL in the LUBT010 treatment arm and 6.7416 (5.4706) ng/mL in the Lucentis treatment arm. Given the concentrations observed in both treatment arms with numerically lower mean concentrations in the LUBT010 arm, the LUBT010 treatment arm might be slightly underexposed compared to the comparator Lucentis. The mean (SD) serum C_{trough} of ranibizumab before the second and third dose were 0.000 ng/mL in both treatment arms. Hence, as already shown in historic PK profiles reported for ranibizumab, the pre-dose concentrations (C_{trough}) of LUBT010 and Lucentis were non-quantifiable in all the patients.

Upon monthly IVT administration of Lucentis 0.5 mg/eye, serum ranibizumab C_{max}, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/ml. The observed mean outcomes at Day 0 post-dose were much higher for both groups. Furthermore, there are some extreme ranibizumab concentrations observed (e.g. LUBT010: 32.520 ng/mL, Lucentis: 49.232 ng/mL; 2 patients in each study arm). Thus, the observed maximum concentrations of both the treatments were in the concentration range of ranibizumab necessary to inhibit the biological activity of vascular endothelial growth factor by 50% [11-27 ng/mL] as measured in an *in vitro* cellular proliferation assay) [Lucentis SmPC]. According to the safety data, the severity of treatment-emergent (TEAEs) in subjects with serum concentrations greater than 2.90 ng/mL was mostly mild. None of these patients experienced drug-related adverse events and notably, none of these patients reported AEs typically associated with systemic VEGF inhibition, such as thromboembolic events, which is reassuring from a safety perspective. No correlation of high ranibizumab serum levels and a safety risk could be identified.

The applicant conducted a thorough investigation of the analytical run which confirmed that the data obtained is reliable. The analytical run included a blank sample, which was found to be acceptable according to the established criteria, indicating that no contamination occurred during sample processing. Furthermore, all samples were analysed in duplicates, and the %CV of the duplicate samples for all subjects was below 20%, indicating assay consistency.

In summary, although elevated C_{max} concentrations were observed following treatment, ranibizumab serum levels remained below the limit of quantification at trough with multiple dosing. Importantly, the higher PK concentrations observed in these individuals do not appear to correlate with an increased risk of AEs potentially linked to systemic VEGF inhibition (although the sample size was very limited in this study).

Pharmacodynamics

No dedicated (comparative) PD investigations were performed as part of the clinical biosimilarity exercise. This can be accepted by CHMP as there appear to be no laboratory PD markers that could be considered as specific surrogates for clinical efficacy and safety of ranibizumab alone. Nevertheless, the evaluation of the change in retinal thickness (e.g., CFT) addressed the PD aspects of the candidate

biosimilar and was included in the PK study LRP/LUBT010/2022/001. The change in CFT at the end of month 1 and month 3 from baseline was measured descriptively as an exploratory PD endpoint. It has been shown that initial treatment-related changes in CFT are predictive of improvement in VA and that CFT is a more objective endpoint than the BCVA. Therefore, the assessment of CFT should generally be considered as a primary or important secondary endpoint in the pivotal study; this was however not taken into account and represents an uncertainty in the assessment.

At the end of month 1, the mean (SD) change from baseline in CFT was -71.1 (132.7) µm in the LUBT010 arm and -77.0 (77.8) µm in the Lucentis arm. The percentage change from baseline in mean retinal thickness was -15.8 (25.6) % in the LUBT010 arm and -20.5 (19.4) % in the Lucentis arm. The difference (LUBT010- Lucentis) in mean percentage change from baseline at Month 1 was 4.8 (±10.5) % [95%CI (-17.60%, 27.18%), p-value 0.655].

At the end of month 3, the mean (SD) change from baseline in CFT was - 91.1 (135.9) µm in the LUBT010 arm and -101 (107.0) µm in the Lucentis arm. The percentage change from baseline in mean retinal thickness was -21.2 (24.2) % in the LUBT010 arm and -23.8 (22.5) % in the Lucentis arm. The difference in mean percentage change from baseline at Month 3 was 2.6 (±10.4) % [95%CI (-19.38%, 24.54%), p-value 0.808].

No CIs for the absolute difference in change from baseline in mean retinal thickness between the study arms were presented. For CFT, a change of 50 µm has been regarded of relevance and an equivalence margin below 40 µm has been accepted. However, the trial was not powered to show equivalence in any PD endpoint. Both treatments showed overall comparable effects on retinal thickness reduction, indicating a similar effect of LUBT010 and Lucentis on retinal anatomy.

Furthermore, ophthalmologic examinations were performed where the BCVA of the study eye was assessed (as part of the safety evaluation). At the end of month 1, the mean (SD) change in BCVA from baseline was 8.0 (7.1) letters in the LUBT010 arm and 4.5 (5.4) letters in the Lucentis arm. At the end of month 3, the mean (SD) change in BCVA from baseline was 10.7 (3.4) letters in the LUBT010 arm and 7.1 (6.1) letters in the Lucentis arm. LUBT010 performed numerically better than Lucentis, but the difference decreased over time. The study duration is very short; hence, it is not clear whether this initial difference will compensate over time. However, the CHMP agreed that this difference in VA could be due to the small patients' number and is negligible at this stage, as BCVA is measured as the PEP in the pivotal (long-term) study and provided overall positive results.

Immunogenicity

Comparative immunogenicity was assessed as a secondary objective in both clinical studies.

In Study LRP/LUBT010/2022/001, immunogenicity in terms of ADA and NAb was evaluated as a secondary endpoint at baseline and at Day 28, 56, and 84. This is agreed, since the more relevant one-year data for immunogenicity were evaluated in the pivotal study LRP/LUBT010/2016/008.

A total of 8 (40%) patients was tested positive for ADA at baseline, with a comparable incidence across both treatment arms.

In the LUBT010 arm, the incidence of treatment-emergent ADAs was 1/10 (10.0%) each at Day 28, 56 and 84 and in the Lucentis arm, the incidence was 1/10 (10.0%) at Day 28, and 2/10 (20%) each at Day 56 and Day 84. Median ADA titres were low and comparable between the LUBT010 and Lucentis treatment arms. While the frequency of ADA-positive patients was comparable between the treatment arms, it is unclear why nearly half of the patients were already ADA-positive prior to study drug administration (a higher-than-expected rate was also found in the pivotal study LRP/LUBT010/2016/008; *find a discussion below*).

All patients were NAb-negative throughout the study. An impact of ADA on safety has not been evaluated, but based on the (limited) data available, no case of drug hypersensitivity has been reported in any of the treatment groups, which is reassuring from a safety perspective.

In Study LRP/LUBT010/2016/008, immunogenicity was a secondary objective and the proportion of ADA-positive patients at the end of 1, 3, 6, 9, and 12 months being a secondary endpoint. In addition, the proportion of NAb among ADA-positive samples was presented.

Among the 600 randomized participants, a high proportion (98.3%) was overall included in the IGS. The ADA incidence at baseline was slightly lower in the LUBT010 arm (25/292, 8.6%) in comparison to the Lucentis arm (30/295, 10.2%) out of which 2 patients in each arm had NAbs. The incidence of treatment emergent ADA was overall comparable between the treatment arms. The median ADA titres were low and comparable at each time point. Treatment emergent NAbs occurred at a low rate and affected mostly 1 or 2 patients, with the highest incidence at Month 12: 21.1% (4/19) in the LUBT010 group and 9.5% (2/21) in the Lucentis group. The observed imbalance is likely a chance finding due to the low frequency of NAb emergence. Cumulatively, the overall ADA incidence was comparable between treatment groups (16.7% vs 17.8% at Month 12 in the LUBT010 vs Lucentis arm, respectively). The overall NAb incidence was low and comparable between LUBT010 (1.7%) and Lucentis (1.3%) at Month 12.

The impact of ADAs on PK was not evaluated as respective samples were not taken. The NAb-positivity rate was comparable and low. Upon request, subgroup analyses for the primary endpoints by ADA status were provided (please refer to the discussion on clinical efficacy).

Regarding the impact of ADAs on safety, one case of uveitis occurred in a LUBT010-treated ADA-positive patient, for which further information was provided. The event occurred 6 days following the dose at month 7, while the patient was ADA-negative until month 6 and ADA-positive at subsequent measurement time points (month 9 and month 12). As the event was transient, occurred in temporal relationship to the IVT administration and did not reoccur upon subsequent dosing, the applicant’s conclusion that the event is rather linked to the IVT injection procedure than to the emergence of ADAs can be followed. Three patients reported drug hypersensitivity, two ADA-negative patients (1 in each treatment arm) and one in a Lucentis-treated ADA positive patient. However,the hypersensitivity reactions were due to another drug. Overall, no clear pattern among ADA-positive patients was apparent but also the overall low number of ADA-positivity has to be considered (25 patients LUB010, 31 patients Lucentis), which impedes the interpretation of results and robust conclusions regarding the ADA impact on safety.

In summary, the presented immunogenicity results indicate comparable ADA incidence with a low proportion of NAbs. However, the ADA-positivity at baseline appears generally higher than expected based on the pre-treatment incidence of historic Lucentis data (0% to 5% across treatment groups, Lucentis USPI 2024). Furthermore, in the pivotal study LRB/LUBT010/2016/008, the detected ADA rate with monthly treatment appears in the upper range or even above the reported incidences with historical Lucentis treatment (approximately 1% to 9% of patients after monthly dosing with Lucentis for 6 to 24 months, Lucentis USPI 2024) or in comparison to published results on LUBT010 (Singh 2022, doi: 10.4103/ijo.IJO_2118_21). Therefore, an investigation was conducted to check the validity of the entire immunogenicity dataset. Robust assay performance was demonstrated. According to the applicant's response, ADA positive samples at baseline may be attributed to the presence of other non-specific binding factors. Given the absence of any difference in the cumulative incidence of antibodies between the two treatment arms, and the low likelihood of identifying a definitive cause, no further investigation is pursued by CHMP. Despite the unclear background of this observation, the increased incidence of ADA positivity was balanced between the study arms; thus, equivalent immunogenicity can be assumed.

5.2.6.2. Conclusions

Comparative PK was assessed exclusively in the stand-alone study LRP/LUBT010/2022/001, which included a total of 20 patients. Pre-dose serum (C_{trough}) levels of both treatments were undetectable. Although peak concentrations exceeded the threshold for VEGF inhibition, no systemic safety concerns were observed, indicating that higher C_{max} values did not lead to increased adverse events.

A comparable decrease in retinal thickness was observed in the supportive study; however, the lack of an anatomical endpoint in the pivotal study represents an uncertainty.

Based on the available (limited) data, there were no notable differences in immunogenicity between the LUBT010 and Lucentis groups over time. The issue of higher-than-expected ADAs remains as an uncertainty. However, the increased incidence of ADA positivity noted in study LRB/LUBT010/2016/008 was balanced between the study arms; thus, equivalent immunogenicity can be assumed.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

5.3.2. Main study

5.3.2.1. LRP/LUBT010/2016/008

5.3.2.1.1. Study 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

5.3.2.1.2. Study design

This was a global, Phase 3, double-blind, randomized, controlled clinical study. The objective of the study was to compare the efficacy, safety, and immunogenicity of LUBT010 to that of Lucentis in patients with neovascular AMD.

The study consisted of the following:

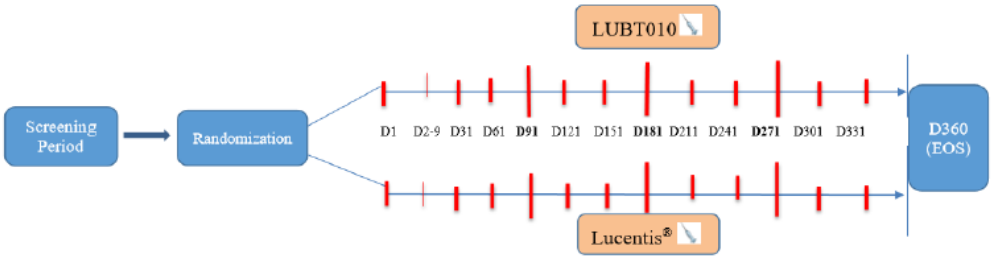
- Screening Period (maximum 28 days)
- Treatment and Assessment Period (12 months)
    - Day 1 (Randomization and first dose of study drug)
    - Safety Visit: Day 2 to 9 (on any day from Day 2 to Day 9, added in Protocol Version 2.0, Appendix 16.1.1)
    - Treatment visits (± 2 days): Day 31 (second dose), and thereafter monthly for a total of 12 months (ie, 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) - EOS

The total study duration for each patient was approximately 13 months.

Figure 1: Study schema



Abbreviations: D=Day, EOS=End of Study.
Lucentis® or LUBT010 injection was 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 visited the study center for a safety visit after the first dose on any day during Day 2 to Day 9. A post injection visit/ telephonic safety assessment after every injection was done as deemed necessary by the Investigator. Day 331 was the End of Treatment (EOT) visit and Day 360 was the EOS visit.
Efficacy and Safety assessments were done at monthly visits. Immunogenicity testing was 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).

Treatment

The investigational biosimilar (LUBT010) and the reference medicinal product (EU-approved Lucentis) were chosen as trial interventions in the current study. The dose chosen for the study was 0.5 mg administered via IVT injection once a month, which is the approved and recommended dose of Lucentis for this indication.

Table 14: Study drug details

Study drug name:	LUBT010	EU-approved Lucentis®
Dose:	0.05 mL of 10 mg/mL ranibizumab	0.05 mL of 10 mg/mL ranibizumab
Dosage form and strength:	2.3 mg of ranibizumab in 0.23 mL solution	2.3 mg of ranibizumab in 0.23 mL solution
Route of administration	Intravitreal injection	Intravitreal injection
Packaging and labeling:	Single-use, 2-cc glass vial, packaged individually in cartons along with syringes and needles. The packs were labeled as per regulatory requirements and each pack had a unique identification number.	Single-use, 2-cc glass vial, packaged individually in cartons along with syringes and needles. The packs were labeled as per regulatory requirements and each pack had a unique identification number.
Storage:	To be refrigerated at 2°C-8°C (36°F-46°F) at all times and protected from light.	To be refrigerated at 2°C-8°C (36°F-46°F) at all times and protected from light.
Source:	Manufacturer: Lupin Limited (Biotech Division), Gat No: 1156, Village Ghotawade, Taluka Mulshi, Pune, Maharashtra, India– 412115	Sourced from: Novartis Europharm Limited Vista Building, Elm Park, Merrion Road Dublin 4, Ireland. (Marketing Authorization Holder in UK)
Batch numbers:	Y200095, Y990022, Y990021, and Y200069.	SAAJ9, SVP94, and SDJN8.

Prohibited medication

The following medications were not permitted during the study:

- Other therapies for the treatment of AMD, including but not limited to verteporfin PDT, pegaptanib, bevacizumab, aflibercept or brolucizumab were not permitted in the study eye.
- Anti-VEGF therapy, other than ranibizumab (approved innovator product) for treatment of exudative AMD in the respective country, was not permitted in the non-study eye.
- Other biologics were not permitted.
- Any other experimental therapy for treatment of AMD was not permitted in either eye.

Concomitant medication

The following medications were permitted during the study:

- Any other medications/treatments required by the patient and not expected to interfere with study assessments were allowed on a case-by-case basis and as deemed appropriate by the Investigator.
- Therapies such as thermal laser and verteporfin PDT for AMD could have been 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) in the non-study eye was permitted when deemed to be clinically justified in the opinion of the Investigator (added in Protocol Version 2.0).
- Supplementation (non-investigational treatments) with antioxidants and minerals (eg, lutein zeaxanthin or beta carotene, Vitamin C, E, and zinc) were permitted.

Randomisation and blinding

On day 1, eligible patients were randomized on in a 1:1 ratio to receive either LUBT010 or Lucentis as an IVT injection.

This study was double-blinded. The blind was maintained by utilizing packaging for LUBT010 with similar appearance to that of Lucentis. Investigators/other staff involved in the study and patients were blinded to the treatment arm during the study.

The randomization code was not to be broken except in medical emergencies, when the appropriate management of the patient required knowledge of the treatment arm, or to meet regulatory requirements (e.g., in the case of serious adverse event [SAE] or death). If possible, a discussion between the Investigator and Sponsor study team and/or the medical expert was to be conducted prior to breaking the randomization code.

Randomization codes indicating the treatment assigned to each randomized patient, was available to the Investigator/study centre staff and the following procedures were followed, if unblinding became necessary.

If the blind was broken, the Investigator was to document the date, time, and reason for unblinding and report the same to the Sponsor. The affected patient/s were to be discontinued from the study immediately by the Investigator and the EOS visit assessments were to be performed.

The blind could have been broken and unblinded safety information could have been provided to the regulatory authority, if requested by the regulatory agency. In such cases, the patient was to continue participation in the study.

Patient population

Approximately 82 sites across Bulgaria, India, Hungary, Poland, the United States of America, Slovakia, and the Russian Federation, having ophthalmologists who were experienced in diagnosing and treating nAMD, and where adequate facilities were available for conduct of trial, were selected for the study.

Inclusion Criteria

Patients who fulfilled all of the following criteria were included in the study:

1. Ambulatory male or female patients with age ≥50 years at the time of screening who were capable of understanding and giving written informed consent.
2. Primary or recurrent (anti-VEGF naïve) active CNV (defined as any leakage detected on fluorescein angiography/fundus FA) lesions involving the foveal centre 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 were of non-childbearing potential (surgically sterile or menopausal), OR, if of childbearing potential using effective birth control measures and non-pregnant and non-lactating during the study and 3 months after the last dose.

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

1. Known hypersensitivity to ranibizumab or any of the components of the study medication.
2. Known history of allergy to fluorescein dye.
3. Scar, fibrosis, or atrophy involving the centre of the fovea in the study eye as assessed by FA (confirmed by independent central reading centre).
4. Subretinal haemorrhage in the study eye that involved the centre of the fovea, the size of the haemorrhage was either ≥50% of the total lesion area or ≥1-disc area (DA) in size (confirmed by independent central reading centre).
5. Total lesion area ≥12.0-DA in size (including blood, scars, and neovascularization) as assessed by FA in the study eye (confirmed by independent central reading centre).
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 were legally institutionalized.
8. Any other pathology involving the CNV lesion like retro-foveolar atrophy or permanent structural damage to fovea or fibrosis/ haemorrhage involving fovea >50% of lesion area of study eye that could have affected the efficacy of the study medication.
9. Vitreous haemorrhage 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 centre).
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 required 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 IVT 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 PDT involving the foveal centre in the study eye within 5 years prior to randomization.
14. Previous treatment with verteporfin 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 IVT steroids (e.g., triamcinolone, anecortave acetate) in the study eye within 3 months prior to randomization.
16. Previous treatment with IVT steroid implant (e.g., 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 study of investigational drugs within 30 days or as prescribed in that study (whichever was later) preceding the initial study treatment.
21. Patients with DME and/or background or proliferative retinopathy were excluded. Likewise, any patient with significant posterior subcapsular cataract was also excluded.
22. Choroidal neovascularization 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 have either required medical or surgical intervention during the 12-month study period or that could have contributed 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 was to be based on the opinion of the Investigator.
25. Any patient with cloudy media from any cause, that prevented adequate visualization of the fundus with indirect ophthalmoscopy were excluded.
26. Patients with seropositivity for hepatitis B, hepatitis C, human immunodeficiency virus 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 have affected interpretation of the results or contraindicated the use of ranibizumab or rendered 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.

Study assessments

Efficacy measurements

BCVA was measured in terms of the number of letters a patient could correctly read on an eye chart; hence an increased score indicated improvement in visual acuity.

For this study, the ETDRS chart (including original Sloan letter chart or number chart) was used for visual acuity measurement. Testing was required to be done prior to dilating eyes with refraction error corrected with lenses. BCVA assessment was to begin at a starting distance of 4 meters.

The National Eye Institute Visual Function Questionnaire 25-Item (NEI VFQ-25) Version 2000 was administered by the Interviewer at baseline (Day 1), 3, 6, and 12 months, which was a measure of subjective response and complimented the objective findings of BCVA.

Immunogenicity Measurements

Immunogenicity was assessed as a secondary endpoint, in terms of ADAs and NAbs at the end of 1, 3, 6, 9, and 12 months.

Safety Measurements

The following safety parameters were assessed:

- AE assessment, ocular and non-ocular (as per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE version 5.0])
- Ophthalmic examination
- Physical and systemic examination
- Vital signs
- ECGs
- Laboratory parameters: Blood (haematology and biochemistry) and urinalysis

5.3.2.1.3. Objectives and estimands

Primary objective

Primary objective

To demonstrate the equivalence in efficacy of LUBT010 to Lucentis in terms of visual acuity, in patients with neovascular AMD.

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 efficacy endpoint

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

No formal statistical testing for equivalence was planned for secondary and exploratory endpoints.

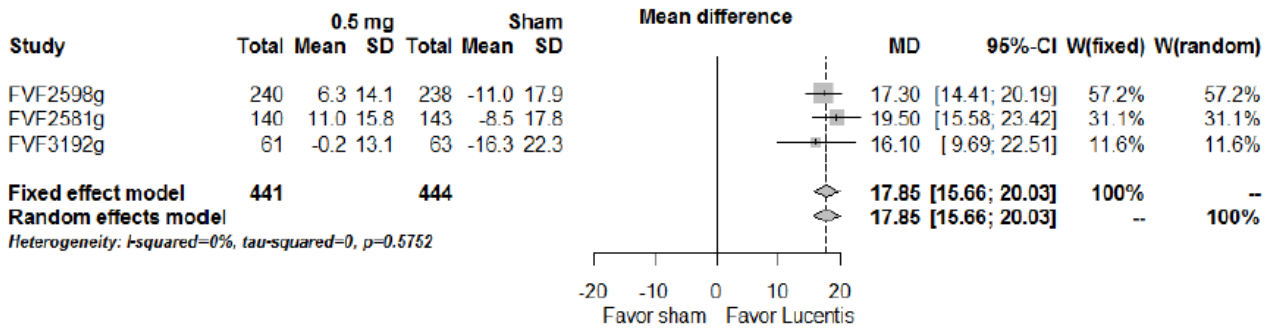
Statistical hypothesis

Equivalence of efficacy between LUBT010 and Lucentis was to be declared if the 95% CI for the difference in mean BCVA at 12 months between the treatment groups (analysed using an analysis of covariance (ANCOVA) model, hence these are the least squares (LS) means) fell fully within the two-sided equivalence margin of (-4,4) letters.

Margin justification for BCVA at Month 12

A statistical justification for this equivalence margin is also provided; specifically, a fixed effect meta-analyses of data from 0.5 mg ranibizumab versus sham treatment groups with a comparable dosing regimen from the filing of the originator Lucentis (studies FVF2598g MARINA, FVF2581g, and FVF3192g PIER) was performed. Month 12 change from baseline of BCVA was used as the endpoint. A mean difference of 17.9 letters [95% CI 15.7-20.0] was found. 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 letter.

Figure 2: Meta-analysis



Margin justification for BCVA at Month 3

In order to determine the margin for equivalence, the results from three studies were used (MARINA, ANCHOR, PIER). Based on the publications for these trials, the mean change from baseline to month 3 and its SD were estimated. Because the results are displayed in figures rather than in tables, the estimates of the SDs from all three studies and the estimates of the mean changes from PIER are approximate rather than exact. These results are displayed in **Table** 20. Using these results, a pooled estimate of the treatment difference and the 95% CI for the treatment difference were obtained by fitting an analysis of variance (ANOVA) model with change from baseline as the dependent variable and with factors for study and treatment group. The LS means for estimating the mean changes from baseline in each treatment group are 6.38 for ranibizumab and - 4.56 for control. The LS mean estimate of the treatment difference is 10.94 with two-sided 95% CI (9.30, 12.58). Based on a lower confidence bound of 9.3 letters, an equivalence margin of 4 letters would preserve 57% of the treatment effect and hence chosen for sample size calculation. The estimates of the true SD of the change in BCVA from baseline to month 3 range from 11.37 to 12.18 for active arm and 11.37 to 17.22 for placebo/SHAM arm, SD of 14.5 was chosen for sample size estimation.

Table 15: Pooled treatment difference to estimate equivalence margin

Study	Group	Number of Patients	Mean	Standard Deviation	Treatment Difference
MARINA	Ranibizumab	240	5.90	11.37	9.60
	Control	238	-3.70	11.37	
ANCHOR	Ranibizumab	140	10.00	12.18	12.50
	Control	143	-2.50	13.54	
PIER	Ranibizumab	61	4.18	11.87	12.55
	Control	63	-8.37	17.22	

Estimand for the primary objective

Table 16: Estimands for the primary objective

Population	Patients with nAMD who meet the inclusion criteria, who might after the start of the study take prohibited medication or discontinue treatment under any treatment assignment. The population was defined as patients aged ≥50 years, with primary or recurrent (anti VEGF-naïve) active CNV lesions involving the foveal centre secondary to AMD in any one of the eyes and BCVA in the study eye, using ETDRS testing, between 20/40 and 20/200 (Snellen equivalent), both inclusive, before pupil dilation.
Treatment condition	Comparison of patients randomly assigned to the monthly IVT injection of LUBT010 0.5 mg (0.05mL of 10 mg/mL ranibizumab) or the monthly IVT injection of Lucentis 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) treatment group, regardless of treatment discontinuation and use of additional medication.
Endpoint (variable)	Mean change in BCVA from baseline in the study eye at the end of 12 months, assessed using the ETDRS chart regardless of intercurrent events.
Population-level summary	Difference in mean change in BCVA from baseline in the study eye at the end of month 12 between LUBT010 and Lucentis arms.
Intercurrent events and strategy to handle them	
Use of prohibited medication	Treatment policy
Treatment discontinuation	Treatment policy

The clinical question of interest was to investigate whether monthly IVT injection of 0.5 mg of LUBT010 and Lucentis in patients with AMD has the same average effect on the BCVA score after a full year of treatment, regardless of whether patients discontinued treatment or started taking prohibited medication (i.e. these intercurrent events were handled using a treatment policy).

Statistical methods for estimation and sensitivity analysis on primary estimand

Analysis Sets

The full analysis set (FAS) consisted of all randomized patients who received at least one dose of a study drug and had a baseline and one post baseline BCVA measurement; this was the primary population for analysis.

The Per Protocol Analysis Set included all patients in the FAS with no major protocol deviations that could impact the assessment of primary efficacy endpoint and excluded all discontinued patients for whom the primary efficacy endpoint is missing.

Analysis Model for the Primary Efficacy Endpoint (Incl. Missing Data Handling)

The primary efficacy analysis for mean change in BCVA from baseline in the study eye at the end of 12 months, assessed using the ETDRS chart, was performed in the FAS using an ANCOVA model with treatment group as a fixed effect, baseline BCVA and age as covariates, and iris colour (light coloured, not light coloured) as a stratification factor. The two-sided 95% CI for the treatment difference between LUBT010 or Lucentis was calculated, and equivalence planned to be declared if this CI was fully contained within the predetermined equivalence margin of (-4, 4) (i.e. then the null hypothesis that LUBT010 was inferior or superior to Lucentis was considered rejected). Missing data for the

primary efficacy analysis was assumed missing at random (MAR) and was imputed using multiple imputation (MI) based on a regression approach assuming a monotone missingness pattern for each treatment arm separately.

Additionally, descriptive summaries were presented for observed and mean change in BCVA from baseline in the study eye at the end of 12 months by treatment groups. As part of this, the mean change in BCVA (±SD) was plotted at each post-baseline visit through month 12 for each treatment group.

Supportive and Sensitivity Analyses for the Primary Efficacy Endpoint

Sensitivity Analysis

To assess the robustness of the MAR assumption in the primary efficacy analysis, a sensitivity analysis was performed; specifically, a tipping point analysis: first, missing values for month 12 were imputed using regression-based MI assuming monotone missingness under the missing not at random (MNAR) assumption with a shift $\delta>0$ at each treatment. Specifically, a total of 1000 imputed datasets were created. Then, for patients in the LUBT010 treatment arms only, the imputed value at month 12 was perturbed by a delta value ranging from -3.5 to 3.5 in increments of 0.5. Next, the final multiple-imputed dataset with all missing values filled was analysed using a linear mixed model with treatment as a fixed effect, baseline BCVA and age as covariates, and iris colour as a stratification factor. Finally, the results for the treatment effect from the 1000 datasets were combined using Rubin's rule. If the combined results did not change the conclusion of equivalence of LUBT010 and Lucentis, it was planned that a larger delta would be chosen, and the procedure repeated until the tipping point was found (i.e. when the test for equivalence returned a $p > 0.05$). The applicant ended up examining tipping point ranges up to (-20,20).

Supportive Analyses

As a first supportive analysis, the primary efficacy analysis was repeated in the PPS, but without imputation of any missing values.

The second supportive analysis for the primary efficacy endpoint consisted of applying a mixed model for repeated measures (MMRM) with an unstructured covariance matrix in both the FAS and PPS; treatment arm, visit, and the treatment by visit interaction were specified as fixed effects, iris colour (light coloured, not light coloured) as a stratification factor, a baseline BCVA and age as covariates, and patient as a random effect.

Secondary objectives

Secondary objectives

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

Safety endpoints

- AE assessment, ocular and non-ocular
- Ophthalmic examination
- Physical and systemic examination
- Vital signs
- Electrocardiogram

- Laboratory parameters - blood (haematology and biochemistry) and urinalysis

Immunogenicity

Proportion of patients with ADAs at the end of 1, 3, 6, 9, and 12 months.

No formal statistical testing for equivalence was planned or performed for the secondary objectives.

Estimands for the secondary objectives

No estimands were defined for the secondary objectives.

Statistical methods for estimation and sensitivity analysis for secondary endpoints

Analyses for the Secondary Efficacy Endpoints

Missing data for secondary efficacy analyses were not imputed. The mean change in BCVA from baseline in the study eye at the end of 3 months as well as that at the end of 6 and 9 months, assessed using the ETDRS chart, were initially summarised descriptively by treatment arm and time point. Data for both secondary endpoints are presented using n, mean, SD, minimum, median, and maximum. Additionally, the mean change of BCVA (±SD) was be plotted at each post-baseline visit through month 12 for each treatment group. A by-patient listing of refraction assessment, BCVA assessment, and low vision testing was also provided for the RAN set.

Additionally, the same primary analysis ANCOVA model on the FAS and supportive ANCOVA on the PPS as for the primary efficacy endpoint of mean change in BCVA at month 12 was applied to the mean change in BCVA at months 3 and 6. Statistical justification of the same two-sided four letter equivalence margin but at 3 and 6 months was provided in a separate document titled `Justification of Equivalence Margin: Fixed effect meta-analyses of data from 0.5 mg ranibizumab versus sham treatment groups with a comparable dosing regimen from the filing of the originator Lucentis (specifically, studies FVF2598g, FVF2581g, and FVF3192g and studies FVF2598g and FVF2581g, respectively) were performed (since heterogeneity across studies was insignificant). An equivalence margin of 4 letters was determined to preserve 60.8% and 68.5% of the treatment effect at 3 and 6 months from the lower 95% CI of the point estimate derived via the fixed-effect meta-analysis, respectively.

5.3.2.1.4. Results

Participant flow and numbers analysed

First Patient Enrolled: 29 September 2020 (First Patient In)

Last Patient Completed: 09 March 2024

Table 17: Patient disposition (enrolled set)

	LUBT010 n (%)	Lucentis® n (%)	Total n (%)
Number of Patients Screened			1028
Number of Screen Failure Patients			428
Number of patients in Randomized Set (RAN)	299 (100.0)	301 (100.0)	600 (100.0)
Number of patients in Full Analysis Set (FAS)	295 (98.7)	296 (98.3)	591 (98.5)
Number of patients in Per Protocol Analysis Set (PPS)	239 (79.9)	260 (86.4)	499 (83.2)
Number of patients excluded from Per Protocol Analysis Set (PPS)	60 (20.1)	41 (13.6)	101 (16.8)
Reasons for exclusion from Per Protocol Analysis Set (PPS)[a]			
Due to study discontinuation	43 (71.7)	32 (78.0)	75 (74.3)
Major protocol deviation	17 (28.3)	9 (22.0)	26 (25.7)
Efficacy	9 (15.0)	4 (9.8)	13 (12.9)
Other	8 (13.3)	5 (12.2)	13 (12.9)
Number of patients in Safety Analysis Set (SAF)	299 (100.0)	301 (100.0)	600 (100.0)
Number of patients in Immunogenicity Analysis Set (IGS)	293 (98.0)	297 (98.7)	590 (98.3)
Patients who completed the study	256 (85.6)	269 (89.4)	525 (87.5)
Patients who discontinued the study	43 (14.4)	32 (10.6)	75 (12.5)
Reasons for discontinuing the study[b]			
Adverse event	6 (14.0)	4 (12.5)	10 (13.3)
Death	3 (7.0)	4 (12.5)	7 (9.3)
Lost to follow up	3 (7.0)	2 (6.3)	5 (6.7)
Pregnancy	0	0	0
Protocol violation	1 (2.3)	4 (12.5)	5 (6.7)
Physician decision	2 (4.7)	0	2 (2.7)
Withdrawal by patient	25 (58.1)	17 (53.1)	42 (56.0)
Study terminated by sponsor	0	0	0
Other	3 (7.0)	1 (3.1)	4 (5.3)

n is the number of patients in each category.
Percentages are based on the number of patients in Randomized Set.
a Percentages are based on the number of patients excluded from Per Protocol Analysis Set.
b Percentages are based on the number of patients in Randomized Set who discontinued the study.

Data sets analysed

A total of 600 patients were randomized in the study (RAN) and all were included in the SAF. Of all randomized patients, 591 (98.5%) patients were included in the FAS, 499 (83.2%) patients were included in the PPS, and 590 (98.3%) patients were included in the IGS.

A total of 9 patients were excluded from the FAS (4 patients in the LUBT010 and 5 patients from the Lucentis arm). These patients were excluded due to lack of baseline (1 patient in the Lucentis arm) or post baseline (8 patients, overall) BCVA measurement.

A total of 101 patients were excluded from the PPS (60 [20.1%] patients in the LUBT010 and 41 [13.6%] patients from the Lucentis arm) (Table 22).

Exposure to study drug

Table 18: Exposure to study drug (safety analysis set)

	Statistics	LUBT010 (N=299)	Lucentis® (N=301)	Total (N=600)
Duration of exposure (days)	n	299	301	600
	Mean (SD)	305.9 (77.27)	311.4 (72.03)	308.7 (74.68)
	Median	331.0	331.0	331.0
	Min - Max	1 - 405	1 - 373	1 - 405
Duration of exposure				
Day 1 to ≤ 91 days	n (%)	16 (5.4)	13 (4.3)	29 (4.8)
Day 92 to ≤ 181 days	n (%)	10 (3.3)	9 (3.0)	19 (3.2)
Day 182 to ≤ 271 days	n (%)	16 (5.4)	10 (3.3)	26 (4.3)
≥ 272 days	n (%)	257 (86.0)	269 (89.4)	526 (87.7)
Extent of Exposure				
Number of Injections				
≤ 1	n (%)	5 (1.7)	6 (2.0)	11 (1.8)
> 1 - ≤ 3	n (%)	10 (3.3)	5 (1.7)	15 (2.5)
> 3 - ≤ 6	n (%)	13 (4.3)	12 (4.0)	25 (4.2)
> 6 - ≤ 9	n (%)	11 (3.7)	11 (3.7)	22 (3.7)
> 9 - ≤ 12	n (%)	260 (87.0)	267 (88.7)	527 (87.8)

Abbreviations: Max=maximum, Min=minimum, SD=standard deviation.
N is the number of patients in the Safety Analysis Set.
n is the number of patients in each category.
Percentages were calculated based on N.
Duration of exposure (days) derived as last injection administration date – first injection administration date +1.

Deviations from study plan

Changes that were made to the planned analyses and included in the final SAP:

- Estimands were added for the primary efficacy endpoint as per the US-FDA recommendations (including specification of intercurrent events)
- The definition of PPS was broadened to exclude patients for whom primary efficacy endpoint data is missing in addition to patients with major PDs impacting the primary efficacy endpoint analysis.
- A MMRM was proposed as an additional supportive analysis since the BCVA data was longitudinal data, collected monthly throughout the study period up to 12 months.
- The cumulative incidence of treatment-emergent ADA and NAb was added, apart from results by timepoint.

Changes that were made to the planned analyses after unblinding (*ad hoc* analyses):

- The range of the delta shift values in the tipping point analysis were increased from the planned (-3., 3.5) to (-20.0 to 20.0).
- The proportions of patients with improvement in BCVA by at least 5, 10, and 15 letters from baseline to the end of 6 and 12 months were provided, as requested during the presubmission meeting.

Protocol amendments

The original protocol dated 18 July 2017 was amended 7 times.

Number (date of internal approval)	Key details of amendment (Section of this report affected)
Amendments made after the start of patient recruitment	
Protocol Version 1.0 (India Specific), 26 September 2017	The following changes were made as per recommendations by Drug Controller General of India (DCGI): • Optical coherence tomography (OCT) assessments were added for the study eye after each study drug administration (footnote 's' of Table 2 Schedule of assessments). • A provision was added for pro-re-nata (PRN) or treat-and-extend regimen in case the Investigator decided to withhold an injection for potential safety concern based on OCT result (Section 9.3.3.3). • Other retino-vascular diseases affecting the macula during the study were added to the ocular criteria for treatment discontinuation (Section 9.3.3.2).
Protocol Version 1.1 (India Specific), 20 January 2020	Approval status of the comparator drug was corrected to EU-approved Lucentis® (Section 9.2).
Protocol Version 1.2 (Global, except India), 18 February 2020	• Schedule for urine pregnancy test was updated (Section 9.5.1). • Provision was made, for any other laboratory tests to be performed if deemed necessary by the Investigator or required by local regulations during the course of the study (Section 9.5.1).
Protocol Version 2.0 (Global), 22 July 2020	• Updates were made to statistical methods, model used for analysis, and the confidence intervals assessed, as per Regulatory consultations for US and EU regions (Section 9.7.1.3). Details of hypothesis and endpoint for PMDA were deleted. • To ensure patient safety, repeat tests were permitted (Section 9.5.1). • In view of the age group of patients, FSH testing was implemented for all female patients (Section 9.5.1). • The postdose observation period was made consistent with IOP measurement period ie, 60 min (± 30 min) (Section 9.5.1). • It was clarified that on drug administration visits, AE assessment was to be performed pre and postdose (Section 9.5.1). • Text on discussion of study design was updated based on available data (Section 9.2). • Ophthalmic examination, study procedures, handling of early discontinuations were clarified (Section 9.5.1). • Provision to withhold dose based on optical coherence tomography results was added to ensure patient's safety (Section 9.5.1). • Anti-VEGF treatment of fellow eye was permitted (Section 9.4.5). • It was clarified that the study eye was to receive study drug only (Section 9.4.5). • It was clarified that abnormal values in ECG assessments were to be clinically correlated by the Investigator and assessed for significance (Section 9.5.1.3). • Handling of missing data was updated based on input from regulatory consultations (Section 9.7.1.3).
Protocol Version 2.1 (Global), 20 April 2021	• New section was added for risk assessment related to COVID-19 pandemic as per EMA guidance (Section 9.1).
Protocol Version 2.2 (Global), 19 May 2022	• Specific details regarding ETDRS chart were added for clarity (Section 9.5.1.1). • A new section was added to describe possible reasons and subsequent actions to be taken in case of withdrawal and discontinuation of patients (Section 9.3.3.2). • Clarifying footnote regarding syphilis confirmatory testing was added (Section 9.5.1).
Protocol Version 3.0 (India Specific), 13 February 2023	• Country level (India specific) amendment to provide justification for seeking import license for Lucentis® (CSR not affected).

Protocol Deviations and Quality Tolerance Limits

Table 19: Summary of important protocol deviations (randomized set)

	LUBT010 (N = 299) n (%)	Lucentis® (N = 301) n (%)	Total (N = 600) n (%)
Patients with any Protocol Deviation	266 (89.0)	281 (93.4)	547 (91.2)
Patients with any Major Deviation	35 (11.7)	26 (8.6)	61 (10.2)
Concomitant Medication	0	2 (0.7)	2 (0.3)
Efficacy	13 (4.3)	8 (2.7)	21 (3.5)
Inclusion Exclusion Criteria	6 (2.0)	5 (1.7)	11 (1.8)
Informed Consent and Process	0	3 (1.0)	3 (0.5)
IP Administration	2 (0.7)	0	2 (0.3)
Other Criteria	8 (2.7)	5 (1.7)	13 (2.2)
Safety	4 (1.3)	4 (1.3)	8 (1.3)
Study Procedures	1 (0.3)	0	1 (0.2)
Patient IP Compliance	3 (1.0)	0	3 (0.5)

N is the number of patients in the Randomized Set. n is the number of patients in each category. Percentages were calculated based on N.
Protocol deviations recorded for subject specific are only included and not site-specific deviations.
Patients may have multiple protocol deviation criteria and hence counted only once under each criterion.

Quality Tolerance Limit - Rate of Treatment Discontinuation of Randomized Patients

A drop-out rate of 7% was assumed during sample size determination, however the actual drop-out rate observed was 12.5%. Hence, the QTL "rate of treatment discontinuation of randomized patients" of up to 12% drop-out rate was met. However, this did not impact the primary analysis planned in the FAS, which consisted of 591 (98.7%) patients.

Baseline data

Table 20: Demographic characteristics (randomized set)

	Statistics	LUBT010 (N=299)	Lucentis® (N=301)	Total (N=600)
Age (years)	n	299	301	600
	Mean (SD)	73.2 (8.75)	73.5 (7.90)	73.3 (8.33)
	Median	75.0	74.0	74.0
	Min - Max	51 - 93	52 - 94	51 - 94
Gender				
Male	n (%)	148 (49.5)	155 (51.5)	303 (50.5)
Female	n (%)	151 (50.5)	146 (48.5)	297 (49.5)
Race				
American Indian or Alaska Native	n (%)	0	0	0
Asian	n (%)	158 (52.8)	147 (48.8)	305 (50.8)
Black or African American	n (%)	0	0	0
Native Hawaiian or Pacific Islanders	n (%)	0	0	0
White	n (%)	141 (47.2)	153 (50.8)	294 (49.0)
Other	n (%)	0	1 (0.3)	1 (0.2)
Latino#	n (%)	0	1 (100.0)	1 (100.0)
Ethnicity				
Hispanic or Latino	n (%)	5 (1.7)	6 (2.0)	11 (1.8)
Not Hispanic or Latino	n (%)	293 (98.0)	295 (98.0)	588 (98.0)
Not Reported	n (%)	0	0	0
Unknown	n (%)	1 (0.3)	0	1 (0.2)
Weight (kg)	n	299	300	599
	Mean (SD)	69.25 (13.696)	70.58 (14.319)	69.91 (14.016)
	Median	68.00	70.00	68.10
	Min - Max	40.9 - 128.0	38.0 - 133.6	38.0 - 133.6

Abbreviations: Max=maximum, Min=minimum, SD=standard deviation.
N is the number of patients in the Randomized Set. n is the number of patients in each category. Percentages were calculated based on N.
Percentages were based on the number of patients in the Randomized Set with Race collected as "Other".

Table 21: Baseline characteristics – study eye (randomized set)

	Statistics	LUBT010 (N=299)	Lucentis® (N=301)	Total (N=600)
BCVA by ETDRS chart	n	299	300	599
	Mean (SD)	53.7 (12.71)	52.5 (12.61)	53.1 (12.66)
	Median	55.0	54.0	55.0
	Min - Max	22 - 77	18 - 76	18 - 77
Iris Color				
Light Colored	n (%)	106 (35.5)	107 (35.5)	213 (35.5)
Not Light Colored	n (%)	193 (64.5)	194 (64.5)	387 (64.5)
Intraocular pressure (IOP) measurement	n	299	301	600
	Mean (SD)	15.0 (2.70)	15.0 (2.72)	15.0 (2.71)
	Median	15.0	15.0	15.0
	Min - Max	8 - 25	8 - 26	8 - 26

Abbreviations: BCVA=Best Corrected Visual Acuity, ETDRS=Early Treatment Diabetic Retinopathy Study, Max=Maximum, Min=Minimum, SD=Standard Deviation.
N is the number of patients in the Randomized Set. n is the number of patients in each category. Percentages were calculated based on N.

Prior and concomitant medication

In line with the reported medical and procedural history, most used prior medications classified by Anatomical Therapeutic Chemical (ATC) class was Anticholinergics (282 [94.3%] patients in the LUBT010 arm and 282 [93.7%] patients in the Lucentis arm): tropicamide (201 [67.2%] patients in the LUBT010 arm and 206 [68.4%] patients in the Lucentis arm), phenylephrine hydrochloride/tropicamide (46 [15.4%] patients in the LUBT010 arm and 43 [14.3%] patients in the Lucentis arm), and phenylephrine/tropicamide (34 [11.4%] patients in the LUBT010 arm and 34 [11.3%] patients in the Lucentis arm).

Prohibited medications: In the Lucentis arm, 2 patients received prohibited medications during the study and these were reported as major protocol deviations: one patient received Avastin (bevacizumab) for treatment of AE (fellow eye converted to wet AMD) and another patient received Eylea (aflibercept) for treatment of non-study eye.

Treatment compliance

Table 22: Treatment compliance (safety analysis set)

	Statistics	LUBT010 (N=299)	Lucentis® (N=301)	Total (N=600)
Overall compliance	n	299	301	600
	Mean (SD)	98.88 (4.039)	98.16 (6.109)	98.52 (5.190)
	Median	100.00	100.00	100.00
	Min - Max	71.4 - 100.0	50.0 - 100.0	50.0 - 100.0
Compliance				
<75%	n (%)	2 (0.7)	5 (1.7)	7 (1.2)
≥75%	n (%)	297 (99.3)	296 (98.3)	593 (98.8)

Abbreviations: Max=Maximum, Min=Minimum, SD=Standard Deviation.
N is the number of patients in the Safety Analysis Set. n is the number of patients in each category. Percentages were calculated based on N. Overall Compliance = (Number of planned injections taken/total number of planned injections) × 100.

Outcomes and estimation

Primary Efficacy Endpoint

Mean Change in BCVA at 12 months (FAS)

Table 23: Analysis of mean change in BCVA from baseline in the study eye at the end of 12 months – US-FDA and EMA (FAS)

Visit	Treatment	Mean (SE)	SD	Min	Median	Max	LS Mean (SE)	FDA 90% CI	EMA 95% CI
Baseline	LUBT010 (N=295)	53.81 (0.739)	12.695	22	55.00	77			
	Lucentis® (N=296)	52.55 (0.736)	12.671	18	54.00	76			
Month 12									
Actual	LUBT010 (N=295)	65.54 (0.886)	14.174	16	67.00	94			
	Lucentis® (N=296)	64.19 (0.858)	14.051	16	65.00	90			
Change from Baseline	LUBT010 (N=295)	11.34 (0.728)	11.648	-36	11.00	52	11.17 (0.689)	(10.04, 12.30)	(9.82, 12.52)
	Lucentis® (N=296)	11.63 (0.687)	11.252	-22	11.00	45	11.14 (0.680)	(10.02, 12.26)	(9.81, 12.47)
	Difference (LUBT010- Lucentis)						0.03 (0.945)	(-1.52, 1.58)	(-1.82, 1.88)

Abbreviations: BCVA=Best Corrected Visual Acuity, CI=confidence interval, EMA=European Medicines Agency, US-FDA=United States-Food and Drug Administration, LS mean= Least Squares mean, Max=maximum, Min=minimum, SD=standard deviation, SE=standard error.
N is the number of patients in the Full Analysis Set.
Inferential statistics are based on analysis of covariance (ANCOVA) model with the baseline BCVA, Age as covariates and treatment as fixed factors and iris color (light colored, not light colored) as a stratification factor.
Therapeutic equivalence (FDA) was to be declared if the 2-sided 90% CI of the difference of BCVA LS mean changes from baseline at Month 12 between LUBT010 and Lucentis® lied within the pre-defined equivalence margin of (-4, 4). Therapeutic equivalence (EMA) was to be declared if the 2-sided 95% CI of the difference of BCVA LS mean changes from baseline at Month 12 between LUBT010 and Lucentis® lied within the pre-defined equivalence margin of (-4, 4).
Descriptive statistics at Month 12 were based on observed and change from baseline data however LS mean estimates, 90% CI and 95% CI were based on the imputed data. Missing data for Month 12 were imputed by multiple imputation (MI) approach under the assumption of outcome is Missing at Random (MAR).
Baseline was defined as the last valid assessment performed prior to administration of the first dose of study drug.

Mean Change in BCVA at 12 months (PPS)

Table 24: Analysis of mean change in BCVA from baseline in the study eye at the end of 12 months – FDA and EMA (PPS)

Visit	Treatment	Mean (SE)	SD	Min	Median	Max	LS Mean (SE)	FDA 90% CI	EMA 95% CI
Baseline	LUBT010 (N=239)	54.51 (0.813)	12.575	22	56.00	77			
	Lucentis® (N=260)	52.67 (0.782)	12.604	18	54.00	76			
Month 12									
Actual	LUBT010 (N=239)	65.46 (0.930)	14.382	16	67.00	94			
	Lucentis® (N=260)	64.41 (0.876)	14.129	16	65.00	90			
Change from Baseline	LUBT010 (N=239)	10.95 (0.732)	11.322	-36	10.00	45	11.23 (0.690)	(10.10, 12.37)	(9.88, 12.59)
	Lucentis® (N=260)	11.74 (0.703)	11.328	-22	11.50	45	11.63 (0.668)	(10.53, 12.73)	(10.31, 12.94)
	Difference (LUBT010- Lucentis)						-0.39 (0.944)	(-1.95, 1.16)	(-2.25, 1.46)

Abbreviations: BCVA=Best Corrected Visual Acuity, CI=Confidence Interval, EMA=European Medicines Agency, FDA=Food and Drug Administration, LS mean= Least Squares mean, Max=maximum, Min=minimum, SD=standard deviation, SE=standard error.
N is the number of patients in the Per Protocol Analysis Set.
Inferential statistics were based on analysis of covariance (ANCOVA) model with the baseline BCVA, Age as covariates and treatment as fixed factors and iris color (light colored, not light colored) as a stratification factor.
Therapeutic equivalence (FDA) is declared if the 2-sided 90% CI of the difference of BCVA LS mean changes from baseline at Month 12 between LUBT010 and Lucentis® lies within the pre-defined equivalence margin of (-4, 4). Therapeutic equivalence (EMA) is declared if the 2-sided 95% CI of the difference of BCVA LS mean changes from baseline at Month 12 between LUBT010 and Lucentis® lies within the pre-defined equivalence margin of (-4, 4).
As Per Protocol Analysis Set includes patients with non-missing efficacy data, descriptive statistics and inferential statistics was calculated based on observed data.
Baseline was defined as the last valid assessment performed prior to administration of the first dose of study drug.

Secondary Efficacy Endpoints

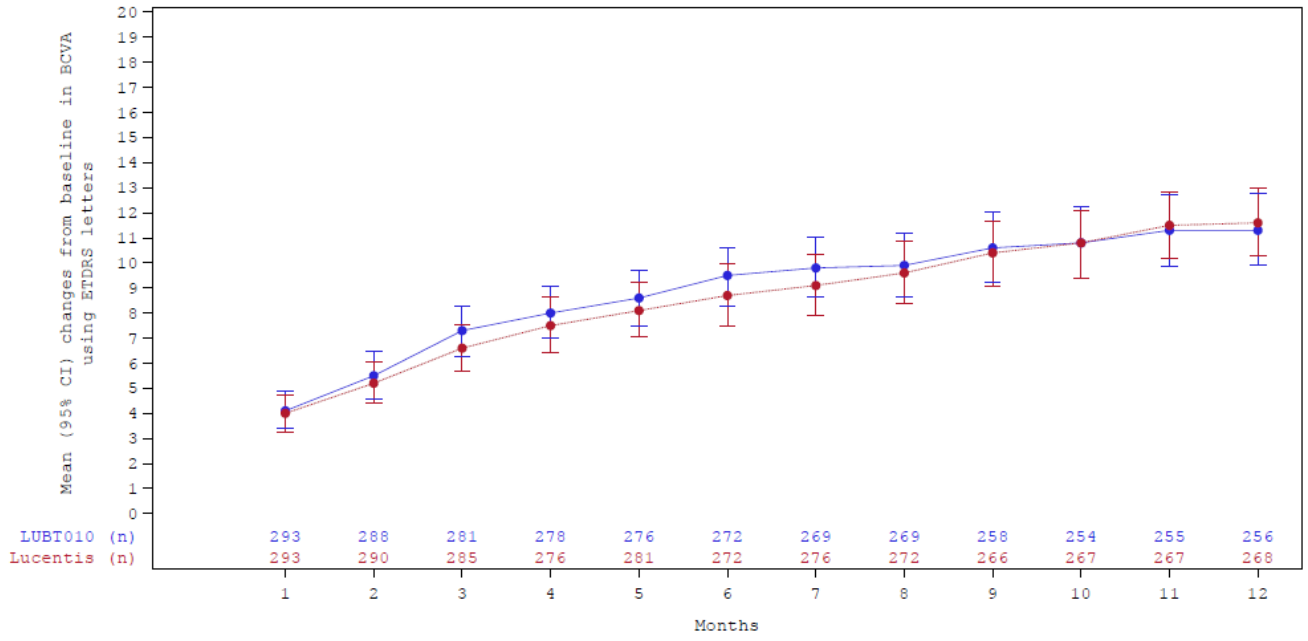
Mean Change in BCVA at 3, 6 and 9 months

Table 25: Summary of change in BCVA from baseline in the study eye at the end of 3, 6 and 9 months (FAS)

		LUBT010 (N=295)		Lucentis® (N=296)	
Visit	Statistics	Actual Values	Change from Baseline	Actual Values	Change from Baseline
Baseline	n	295		296	
	Mean (SD)	53.8 (12.69)		52.6 (12.67)	
	Median	55.0		54.0	
	Min – Max	22 - 77		18 - 76	
Month 3	n	281	281	285	285
	Mean (SD)	60.8 (14.21)	7.3 (8.38)	59.1 (14.37)	6.6 (7.97)
	Median	63.0	7.0	60.0	6.0
	Min – Max	23 - 89	-20 - 40	16 - 85	-21 - 47
Month 6	n	272	272	272	272
	Mean (SD)	63.7 (13.60)	9.5 (9.67)	61.2 (15.09)	8.7 (10.35)
	Median	65.0	9.0	62.5	9.0
	Min – Max	20 - 90	-32 - 45	12 - 91	-24 - 47
Month 9	n	258	258	266	266
	Mean (SD)	64.9 (13.89)	10.6 (11.36)	62.7 (14.57)	10.4 (10.62)
	Median	67.0	10.0	64.0	10.0
	Min – Max	12 - 90	-40 - 47	19 - 89	-20 - 43

Abbreviations: BCVA=Best Corrected Visual Acuity, Max=maximum, Min=minimum, SD=standard deviation.
N is the number of patients in the Full Analysis Set.
n is the number of patients in each category.
Baseline was defined as the last valid assessment performed prior to administration of the first dose of study drug.

Figure 3: Mean change from baseline (95% CI) in BCVA using ETDRS chart at each timepoint (FAS)



BCVA: Best Corrected Visual Acuity, CI: Confidence Interval, ETDRS: Early Treatment Diabetic Retinopathy Study.
n is the number of patients in each category.

Supportive analyses

Table 26: Supportive analysis of MMRM for change in BCVA from baseline to month 12 (FAS)

				LUBT010 vs LUCENTIS			
Visit	Treatment	n	LS Mean (SE)	LS Mean Difference (SE)	95% CI	90% CI	p-value
Month 1	LUBT010 (N=295)	293	4.33 (0.381)				
	Lucentis (N=296)	293	4.14 (0.380)	0.19 (0.526)	(-0.84, 1.22)	(-0.68, 1.06)	0.718
Month 2	LUBT010 (N=295)	288	5.76 (0.455)				
	Lucentis (N=296)	290	5.54 (0.453)	0.22 (0.632)	(-1.02, 1.46)	(-0.82, 1.26)	0.726
Month 3	LUBT010 (N=295)	281	7.26 (0.489)				
	Lucentis (N=296)	285	6.78 (0.487)	0.49 (0.680)	(-0.85, 1.82)	(-0.63, 1.61)	0.473
Month 4	LUBT010 (N=295)	278	8.04 (0.549)				
	Lucentis (N=296)	276	7.66 (0.547)	0.38 (0.766)	(-1.12, 1.89)	(-0.88, 1.64)	0.619
Month 5	LUBT010 (N=295)	276	8.59 (0.571)				
	Lucentis (N=296)	281	8.03 (0.567)	0.56 (0.796)	(-1.00, 2.12)	(-0.75, 1.87)	0.482
Month 6	LUBT010 (N=295)	272	9.50 (0.612)				
	Lucentis (N=296)	272	8.72 (0.609)	0.78 (0.855)	(-0.90, 2.46)	(-0.63, 2.19)	0.360
Month 7	LUBT010 (N=295)	269	9.66 (0.624)				
	Lucentis (N=296)	276	9.00 (0.620)	0.66 (0.872)	(-1.05, 2.38)	(-0.77, 2.10)	0.446
Month 8	LUBT010 (N=295)	269	9.83 (0.639)				
	Lucentis (N=296)	272	9.59 (0.635)	0.24 (0.893)	(-1.52, 1.99)	(-1.24, 1.71)	0.792
Month 9	LUBT010 (N=295)	258	10.46 (0.673)				
	Lucentis (N=296)	266	10.13 (0.667)	0.34 (0.941)	(-1.51, 2.18)	(-1.21, 1.89)	0.721
Month 10	LUBT010 (N=295)	254	10.61 (0.696)				
	Lucentis (N=296)	267	10.49 (0.689)	0.12 (0.972)	(-1.79, 2.03)	(-1.48, 1.72)	0.903
Month 11	LUBT010 (N=295)	255	11.13 (0.684)				
	Lucentis (N=296)	267	11.32 (0.677)	-0.19 (0.955)	(-2.07, 1.68)	(-1.77, 1.38)	0.840
Month 12	LUBT010 (N=295)	256	11.12 (0.703)				
	Lucentis (N=296)	268	11.40 (0.695)	-0.28 (0.981)	(-2.21, 1.65)	(-1.89, 1.34)	0.778

BCVA: Best Corrected Visual Acuity [ETDRS (Early Treatment Diabetic Retinopathy Study) score]; CI: Confidence Interval; LS Mean: Least Square Mean; SE: Standard Error.
N is the number of patients in the Full Analysis Set. n is the number of patients in the corresponding visit.
Inferential statistics are based on Mixed Model of Repeated Measure (MMRM) with fixed effects of treatment group, visit, treatment by visit interaction, Iris color as stratification factor and baseline BCVA value, Age as covariates with patient as random effect.

Table 27: Supportive analysis of MMRM for change in BCVA from baseline to month 12 (PPS)

				LUBT010 vs LUCENTIS			
Visit	Treatment	n	LS Mean (SE)	LS Mean Difference (SE)	95% CI	90% CI	p-value
Month 1	LUBT010 (N=239)	239	4.29 (0.419)				
	Lucentis (N=260)	258	4.17 (0.405)	0.12 (0.573)	(-1.00, 1.25)	(-0.82, 1.07)	0.833
Month 2	LUBT010 (N=239)	237	6.23 (0.477)				
	Lucentis (N=260)	258	5.78 (0.461)	0.46 (0.654)	(-0.83, 1.74)	(-0.62, 1.53)	0.487
Month 3	LUBT010 (N=239)	238	7.48 (0.529)				
	Lucentis (N=260)	256	6.93 (0.510)	0.54 (0.727)	(-0.88, 1.97)	(-0.65, 1.74)	0.454
Month 4	LUBT010 (N=239)	237	8.33 (0.559)				
	Lucentis (N=260)	253	8.11 (0.539)	0.21 (0.769)	(-1.30, 1.72)	(-1.05, 1.48)	0.782
Month 5	LUBT010 (N=239)	236	8.74 (0.576)				
	Lucentis (N=260)	257	8.57 (0.555)	0.17 (0.792)	(-1.39, 1.72)	(-1.14, 1.47)	0.834
Month 6	LUBT010 (N=239)	238	9.64 (0.622)				
	Lucentis (N=260)	252	9.27 (0.599)	0.38 (0.857)	(-1.31, 2.06)	(-1.04, 1.79)	0.660
Month 7	LUBT010 (N=239)	238	9.80 (0.635)				
	Lucentis (N=260)	259	9.61 (0.611)	0.18 (0.875)	(-1.54, 1.90)	(-1.26, 1.62)	0.834
Month 8	LUBT010 (N=239)	239	9.92 (0.657)				
	Lucentis (N=260)	256	10.15 (0.632)	-0.23 (0.905)	(-2.01, 1.55)	(-1.72, 1.26)	0.798
Month 9	LUBT010 (N=239)	236	10.31 (0.685)				
	Lucentis (N=260)	255	10.70 (0.659)	-0.39 (0.945)	(-2.25, 1.47)	(-1.95, 1.17)	0.681
Month 10	LUBT010 (N=239)	236	10.56 (0.708)				
	Lucentis (N=260)	256	11.04 (0.681)	-0.48 (0.976)	(-2.40, 1.44)	(-2.09, 1.13)	0.621
Month 11	LUBT010 (N=239)	237	11.15 (0.693)				
	Lucentis (N=260)	258	11.89 (0.666)	-0.74 (0.955)	(-2.62, 1.14)	(-2.31, 0.83)	0.438
Month 12	LUBT010 (N=239)	239	11.16 (0.716)				
	Lucentis (N=260)	260	11.93 (0.688)	-0.77 (0.987)	(-2.71, 1.17)	(-2.40, 0.86)	0.435

BCVA: Best Corrected Visual Acuity [ETDRS (Early Treatment Diabetic Retinopathy Study) score]; CI: Confidence Interval; LS Mean: Least Square Mean; SE: Standard Error.
N is the number of patients in the Per Protocol Analysis Set. n is the number of patients in the corresponding visit.
Inferential statistics are based on Mixed Model of Repeated Measure (MMRM) with fixed effects of treatment group, visit, treatment by visit interaction, Iris color as stratification factor and baseline BCVA value, Age as covariates with patient as random effect.

Additional analyses

Table 28: Analysis of mean change in BCVA from baseline in the study eye at the end of 3 months and 6 months (FAS)

Visit	Treatment	Mean (SE)	SD	Min	Median	Max	Least Square Mean (SE)	95% CI
Baseline	LUBT010 (N=295)	53.81 (0.739)	12.695	22	55.00	77		
	Lucentis (N=296)	52.55 (0.736)	12.671	18	54.00	76		
Month 3								
Actual	LUBT010 (N=295)	60.85 (0.848)	14.211	23	63.00	89		
	Lucentis (N=296)	59.09 (0.851)	14.372	16	60.00	85		
Change from Baseline	LUBT010 (N=295)	7.27 (0.500)	8.385	-20	7.00	40	7.29 (0.494)	(6.32, 8.26)
	Lucentis (N=296)	6.62 (0.472)	7.971	-21	6.00	47	6.82 (0.490)	(5.86, 7.79)
	Difference (LUBT010- Lucentis)						0.46 (0.679)	(-0.87, 1.79)
Month 6								
Actual	LUBT010 (N=295)	63.66 (0.825)	13.604	20	65.00	90		
	Lucentis (N=296)	61.24 (0.915)	15.092	12	62.50	91		
Change from Baseline	LUBT010 (N=295)	9.46 (0.586)	9.665	-32	9.00	45	9.54 (0.614)	(8.34, 10.74)
	Lucentis (N=296)	8.73 (0.628)	10.350	-24	9.00	47	8.63 (0.610)	(7.43, 9.82)
	Difference (LUBT010- Lucentis)						0.91 (0.845)	(-0.75, 2.57)

Abbreviations: BCVA: Best Corrected Visual Acuity [ETDRS (Early Treatment Diabetic Retinopathy Study) score], CI: Confidence Interval, EMA: European Medicines Agency, Max: Maximum, Min: Minimum, SD: Standard Deviation, SE: Standard Error.
N is the number of patients in the Full Analysis Set.
Inferential statistics are based on analysis of covariance (ANCOVA) model with the baseline BCVA, Age as covariates and treatment as fixed factors and iris color (light colored, not light colored) as a stratification factor.
Therapeutic equivalence is declared if the two-sided 95% Confidence Interval (CI) of the difference of BCVA Least Squares mean (LS mean) changes from baseline at Month 3 and at Month 6 between LUBT010 and Lucentis lies within the pre-defined equivalence margin of (-4 letters, 4 letters).
Missing data for Month 3 and for month 6 were imputed by multiple imputation(MI) approach under the assumption of outcome is Missing at Random (MAR).
Descriptive statistics at month 3 and at month 6 are based on observed and change from baseline data however LS mean estimates, 95% CI and p-value are based on the imputed data.
Baseline is defined as the last valid assessment performed prior to administration of the first dose of study treatment.

Table 29: Analysis of mean change in BCVA from baseline in the study eye at the end of 3 months and 6 months (PPS)

Visit	Treatment	Mean (SE)	SD	Min	Median	Max	Least Square Mean (SE)	95% CI
Baseline	LUBT010 (N=239)	54.51 (0.813)	12.575	22	56.00	77		
	Lucentis (N=260)	52.67 (0.782)	12.604	18	54.00	76		
Month 3								
Actual	LUBT010 (N=239)	61.68 (0.927)	14.305	23	64.00	89		
	Lucentis (N=260)	59.38 (0.893)	14.286	16	60.00	85		
Change from Baseline	LUBT010 (N=239)	7.23 (0.547)	8.435	-20	7.00	40	7.47 (0.529)	(6.43, 8.51)
	Lucentis (N=260)	6.75 (0.515)	8.235	-21	6.00	47	6.92 (0.513)	(5.91, 7.93)
	Difference (LUBT010- Lucentis)						0.55 (0.724)	(-0.87, 1.98)
Month 6								
Actual	LUBT010 (N=239)	64.01 (0.885)	13.654	20	65.00	90		
	Lucentis (N=260)	61.69 (0.935)	14.844	12	63.00	91		
Change from Baseline	LUBT010 (N=239)	9.42 (0.606)	9.355	-32	9.00	45	9.69 (0.620)	(8.47, 10.91)
	Lucentis (N=260)	9.03 (0.651)	10.327	-24	10.00	47	9.08 (0.609)	(7.89, 10.28)
	Difference (LUBT010- Lucentis)						0.61 (0.853)	(-1.06, 2.29)

Abbreviations: BCVA: Best Corrected Visual Acuity [ETDRS (Early Treatment Diabetic Retinopathy Study) score], CI: Confidence Interval, EMA: European Medicines Agency, Max: Maximum, Min: Minimum, SD: Standard Deviation, SE: Standard Error.
N is the number of patients in the Per Protocol Analysis Set.
Inferential statistics are based on analysis of covariance (ANCOVA) model with the baseline BCVA, Age as covariates and treatment as fixed factors and iris color (light colored, not light colored) as a stratification factor.
Therapeutic equivalence is declared if the two-sided 95% Confidence Interval (CI) of the difference of BCVA Least Squares mean (LS mean) changes from baseline at Month 3 and at Month 6 between LUBT010 and Lucentis lies within the pre-defined equivalence margin of (-4 letters, 4 letters).
As Per Protocol Analysis Set includes patients with non-missing efficacy data, descriptive statistics and inferential statistics is calculated based on observed data.
Baseline is defined as the last valid assessment performed prior to administration of the first dose of study treatment.

Exploratory Efficacy Endpoint

Mean Change from Baseline in the NEI VFQ-25 Version 2000 Score at 3, 6, and 12 Months

Table 30: Summary statistics of mean change from baseline of NEI VFQ-25 composite score (FAS)

		LUBT010 (N=295)		Lucentis (N=296)		Total (N=591)	
Visit	Statistics	Actual Values	Change from Baseline	Actual Values	Change from Baseline	Actual Values	Change from Baseline
Baseline	n	294		296		590	
	Mean (SD)	63.11 (20.445)		64.37 (18.825)		63.74 (19.642)	
	Median	63.40		65.09		64.03	
	Min - Max	16.5 - 98.5		19.1 - 98.2		16.5 - 98.5	
Month 3	n	280	279	284	284	564	563
	Mean (SD)	67.44 (19.432)	4.40 (10.449)	68.35 (17.792)	3.78 (11.160)	67.90 (18.613)	4.09 (10.808)
	Median	69.86	3.13	69.50	2.15	69.61	2.50
	Min - Max	16.2 - 100.0	-33.5 - 41.9	20.2 - 98.7	-43.8 - 41.0	16.2 - 100.0	-43.8 - 41.9
Month 6	n	271	270	272	272	543	542
	Mean (SD)	69.06 (18.216)	6.08 (11.715)	70.10 (17.220)	5.84 (13.099)	69.58 (17.715)	5.96 (12.418)
	Median	68.67	4.53	72.11	3.54	71.00	3.97
	Min - Max	13.3 - 100.0	-43.5 - 43.1	20.2 - 99.4	-45.7 - 55.1	13.3 - 100.0	-45.7 - 55.1
Month 12	n	256	255	266	266	522	521
	Mean (SD)	72.71 (18.148)	9.59 (15.966)	73.98 (16.775)	9.25 (15.457)	73.36 (17.457)	9.42 (15.694)
	Median	76.17	6.38	76.63	5.96	76.54	6.25
	Min - Max	14.9 - 100.0	-42.4 - 59.2	25.3 - 100.0	-38.8 - 51.3	14.9 - 100.0	-42.4 - 59.2

Max: Maximum, Min: Minimum, NEI-VFQ-25: National Eye Institute Visual Functioning Questionnaire - 25, SD: Standard Deviation.
N is the number of patients in the Full Analysis Set. n is the number of patients in each category.
Baseline is defined as the last valid assessment performed prior to administration of the first dose of study treatment.

Pre-defined and post-hoc subgroup analyses

Upon request, the applicant performed a post-hoc analysis of the primary endpoint mean change in BCVA from baseline in the study eye at the end of 12 months by treatment-emergent ADA status.

There was a total of 40 patients who tested positive for treatment-emergent ADA at 12 months (LUBT010, n=19; Lucentis, n=21). For this ADA positive subgroup, the LS-mean change from baseline in BCVA was 15.63 letters in the LUBT010 arm and 11.93 letters in the Lucentis arm. The LS-mean treatment difference between LUBT010 and Lucentis arms, was 3.70 with 95% CI (-3.54, 10.93), which is not statistically significant (p=0.307).

For ADA negative subgroup, the LS-mean change from baseline in BCVA was 11.39 letters in the LUBT010 arm and 11.35 letters in the Lucentis arm. The LS-mean treatment difference between LUBT010 and Lucentis arms, was 0.04 with 95% CI (-1.86, 1.94), which is not statistically significant (p=0.967).

Pre-defined and post-hoc sensitivity analyses

A planned sensitivity analysis of mean change in BCVA from baseline in the study eye at the end of 12 months with a set of shift parameters (-3.5 to 3.5) that adjusted for imputed values was provided.

Since with the planned shift parameters (-3.5 to 3.5) the 90% CI (FDA), 95% CI (EMA) of the treatment difference from the ANCOVA analysis model remained within the equivalence margin of (-4, 4), so post hoc sensitivity analysis was performed with a wider set of shift parameters (-20 to 20) for which the 90% and 95% CI of the treatment difference from the ANCOVA analysis model started moving out of the pre-defined equivalence margin of (-4, 4) as provided for FAS.

Results showed that CI values began to move out of the pre-defined equivalence margin of (-4, 4) when using a wider set of shift parameters (-20 to 20), thus achieving the tipping point.

Post hoc analysis excluding the data of subjects enrolled at one Site

As recommended in the integrated inspection report, the Applicant was requested to provide analyses after excluding data from the Country 1 in support of the MAA because the inspection team concluded that this site was considered not compliant with ICH GCP and reported data not trustworthy.

The difference in mean change in BCVA from baseline in the study eye at the end of month 12 between LUBT010 and Lucentis arms was 0.14 95% CI (-1.73, 2.01). In the PPS, the LS mean difference was -0.025 95% CI (-2.13, 1.62).

As for the analysis of mean change in BCVA from baseline in study eye at the end of 3 months and 6 months, the LS mean differences were 0.56 95% CI (-0.78, 1.91) and 1.00 95% CI (-0.67, 2.67), respectively (FAS). In the PPS, the LS mean differences were 0.68 95% CI (-0.75, 2.11) and mean LS 0.73 95% CI (-0.96, 2.42).

Ancillary analyses

Analysis of proportion of patients with improvement in BCVA by at least 5, 10 and 15 letters from baseline to the end of 6 and 12 months

Table 31: Analysis of proportion of patients with improvement in BCVA by at least 5, 10 and 15 letters from baseline to the end of 6 and 12 months (FAS)

Visit Improvement Status by letters	Statistics	LUBT010 (N=295)	Lucentis (N=296)
Month 6			
Improvement in BCVA by			
at least 5 letters	n (%)	229 (77.6)	239 (80.7)
	95% CI	(72.44, 82.25)	(75.78, 85.08)
	p-Value		0.351
at least 10 letters	n (%)	164 (55.6)	168 (56.8)
	95% CI	(49.72, 61.35)	(50.90, 62.48)
	p-Value		0.776
at least 15 letters	n (%)	93 (31.5)	88 (29.7)
	95% CI	(26.26, 37.16)	(24.58, 35.29)
	p-Value		0.636
Month 12			
Improvement in BCVA by			
at least 5 letters	n (%)	245 (83.1)	252 (85.1)
	95% CI	(78.27, 87.15)	(80.56, 88.99)
	p-Value		0.488
at least 10 letters	n (%)	192 (65.1)	204 (68.9)
	95% CI	(59.34, 70.52)	(63.31, 74.15)
	p-Value		0.322
at least 15 letters	n (%)	128 (43.4)	141 (47.6)
	95% CI	(37.66, 49.26)	(41.83, 53.49)
	p-Value		0.300

BCVA: Best Corrected Visual Acuity [ETDRS (Early Treatment Diabetic Retinopathy Study) score], CI: Confidence Interval,
N is the number of patients in the Full Analysis Set. n is the number of patients in each category. Percentages are calculated based on N.
Baseline is defined as the last valid assessment performed prior to administration of the first dose of study treatment.
95% Confidence Interval is based on Clopper-Pearson (Exact) binomial test.
p-value is based on Chi-square test.

Overall discussion and conclusions on clinical efficacy

5.3.2.2. Discussion

The demonstration of biosimilarity between Lupin ranibizumab (LUBT010) and Lucentis rests on one pivotal 12-months Phase 3 efficacy and safety study in nAMD patients to demonstrate therapeutic equivalence (Study **LRP/LUBT010/2016/008**). In addition, the applicant conducted one separate PK study in nAMD patients (Study **LRP/LUBT010/2022/001**) (discussed in detail in the Clinical Pharmacology section), considered as supportive.

Design and conduct of the clinical study

Study LRP/LUBT010/2016/008 was a global, double-blind, randomised study to compare the efficacy safety and immunogenicity of the proposed biosimilar LUBT010 and the originator EU-licensed Lucentis in neovascular AMD patients. The CHMP agreed that the study design is overall adequate and the treatment period of 12 months is deemed sufficiently long to assess efficacy, immunogenicity and safety in the context of biosimilarity.

The choice of EU-Lucentis as reference medicinal product is also endorsed. The investigated treatment regimen of monthly IVT injections and the chosen dose of 0.5 mg ranibizumab is acceptable. Although the usual clinical practise employs rather a treat-and-extend regimen, the monthly dosing with 12 injections is considered a conservative approach as a high cumulative dose is reached. Thus, the study intervention is considered appropriate.

Like Lucentis, LUBT010 is planned to be presented as vial and PFS, while only the vial dosage form has been evaluated in the clinical studies. However, comparability between the vial and the PFS has been demonstrated at the quality level.

The chosen study population of anti-VEGF naïve neovascular AMD patients is considered a sensitive population to detect potential differences in clinical efficacy between the proposed biosimilar and the originator as compared to the indications of DME, RVO, and CNV. Based on the same mechanism of action, extrapolation to all adult indications (DME, PDR, RVO, and CNV) is justified (please see section 10.5 Extrapolation of safety and efficacy).

The inclusion and exclusion criteria are generally in line with those in the clinical trials performed with Lucentis (Lucentis EPAR) and are thus, acceptable for CHMP. The planned study population encompassed patients ≥50 years of age with a baseline visual acuity between 20/40 and 20/200 Snellen equivalent, both inclusive. The applicant mostly followed the EMA scientific advice concerning the study population. Regarding the size of the lesion area, a DA of ≥12.0 in size was set as exclusion criterion. Although in the EMA scientific advice it was pointed out that a meta-analysis of the data from the published studies indicated a higher gain in visual acuity in patients with smaller baseline lesion areas (<4.3 DAs) the applicant did not follow this advice. While a smaller lesion area as cut-off would have been desirable to increase the homogeneity of the study population, the chosen upper limit is in line with the pivotal studies of Lucentis, and therefore acceptable. The summarised baseline data pertaining to the total lesion area per treatment group was requested, as the baseline lesion area affects visual acuity outcome measures. However, respective baseline data were seemingly not documented, although a total lesion area ≥12.0-DA in size was an exclusion criterion. Similarity, baseline data as regards CNV lesion type (classic or occult) were not collected.

Randomisation was performed in 1:1 ratio and was stratified by iris colour (light coloured, not light coloured), but not by country or region. Although stratification by region would have been possible, this is not pursued due to the observed balance between treatment arms in this factor. The process of blinding was adequately described, while protocol deviations mentioning instances of unblinding required further explanation. Upon clarification, it was agreed by CHMP that only a small proportion of study participants were affected (13 out of

600) and the impact on the study conclusions based on these deviations is deemed negligible. However, there was one major finding raised during the conducted EMA routine GCP inspection (Integrated inspection report, EMA/IN/0000263152, 2025), which pertained to the blinding solution and labelling approach. The report notes that "*The Pharmacy Manual v1.0 (dated 01-Jun-2020) was not detailed enough regarding established blinding solution of the study drug. Pharmacy Manual v2.0 was issued on 18-Aug-2023 detailing the importance to adhere to correct IMP management process including blinding*". The update of the Pharmacy Manual was initiated due to the above discussed unblinding events, which considering the trial duration (first patient in: 29 September 2020; last patient completed: 09 March 2024), was conducted rather late in the trial. The major finding particularly concerned the fitness of the blinding solution to detect tampering based on an investigational medicinal product kit presented during the inspection. It is reassuring that events of unblinding were noted during monitoring visits and confined to a small proportion of participating study sites and enrolled patients. However, the inspection report also noted that it remained unclear whether all kits employed in the clinical trial were fit for purpose. The potential extent of unblinding is unknown but does not, on the whole, represent a significant source of uncertainty.

The primary objective, outcome measures, and statistical hypothesis were adequately described. The mean change in BCVA from baseline is a sensitive and clinically relevant endpoint. However, the evaluation of the primary endpoint at month 12 is not considered the most sensitive time point. It was recommended to conduct primary analyses for equivalence before reaching an efficacy plateau, which occurs at 2-3 months for Lucentis (as seen in the ANCHOR and MARINA trials). However, the applicant provided an additional analysis of the difference in mean change of BCVA between the LUBT010 and Lucentis treatment groups after 3 months. The change in BCVA after 3 months is of primary interest due to its higher sensitivity for detecting differences between products. Therefore, the primary analysis after 12 months will be complemented by this additional analysis to ensure a reliable evaluation of biosimilarity across the treatment response range.

Similarity between the two treatments was to be concluded, if the 95% CI of the treatment difference at month 12 fell fully within a pre-defined two-sided equivalence margin of ±4 letters. No clinical justification for this margin was provided. As stated in the EMA scientific advice procedure (EMEA/H/SA/3346/1/2016/III), a 4-letter margin is considered unnecessarily large when considered against the number of letters on average gained from baseline under treatment at the 3 months timepoint and a preferred choice of 3 letters was stated. Since the treatment effect may not fully set in for all patients at 3 months but is expected to plateau well before 12 months, there is an even stronger clinical argument for an equivalence margin of at most 3 letters for the applicant's proposed primary endpoint at 12 months. While the specified 4-letter margin is considered not justified from a clinical point of view, a margin justification was not pursued by CHMP, as both results at 3 and 12 months are within ±3 letters for all provided analyses.

As regards the primary estimand, use of prohibited medication, and treatment discontinuation were considered as intercurrent events. Data collected after occurrence of either type of intercurrent events was included in the analysis (treatment policy approach). Ranibizumab treatment was allowed in the fellow eye, which should also be considered an intercurrent event. Generally, in the setting of an equivalence trial, the treatment policy approach is not necessarily the most adequate strategy for handling intercurrent events.

The secondary endpoints are acceptable as supportive for the primary endpoint, but no anatomical endpoints (e.g. CFT) were evaluated in the pivotal study. The evaluation of CFT is important and, if not the primary endpoint, it should also be considered as key secondary endpoint. While initial treatment induced changes in CFT have been shown to be predictive for improvement in VA, CFT is a more objective endpoint than BCVA. The OCT was performed at the Investigator's discretion at month 3, 6 and 12. The proportion of patients with an OCT procedure was comparable between study arms (~17-27% depending on the time point), while results thereof were not captured. Changes in CFT were evaluated in the Phase 1 PK study. However, due to the small sample size, results can be seen only as supportive, at most. The lack, or limitedness, of an

anatomical endpoint evaluation will remain as an uncertainty for biosimilarity, which needs to be based solely on BCVA changes as regards therapeutic comparability.

The SAP (dated 11 May 2024; last patient completed the study on 09 March 2024) was finalised before unblinding of the data and the database lock was on 13 May 2024. Likewise, the applicant clarified that major protocol deviations were specified prior database lock and unblinding of the data. As for the PPS the exclusion of patients with missing primary efficacy endpoint data was only added in the SAP after the last patient completed the study and not included in the protocol. A PPS analysis excluding patients with major protocol deviations but imputing for patients with missing data for the mean change in BCVA from baseline at month 12 and month 3 was requested (please see below).

The ANCOVA model applied as the primary analysis model to the mean change in BCVA from baseline at month 12 included the treatment group as a fixed effect, baseline BCVA and age as covariates, and iris colour (light coloured, not light coloured) as a stratification factor. Missing data for the primary efficacy analysis was assumed MAR and was imputed using MI. The analysis of the primary efficacy endpoint was repeated with an appropriately specified MMRM which automatically imputes under MAR. The validity of the MAR assumption for missing data was investigated via a tipping point analysis, where a range of perturbation values between (-20,20) were added to the primary endpoint in the LUBT010 treatment arm.

The study protocol was amended 7 times, with 4 amendments prior to the first patient enrolled; most changes were considered minor.

Overall, 600 patients were enrolled and randomised 1:1 to LUBT010 (n=299) and Lucentis (n=301) at 78 study sites across Bulgaria, India, Hungary, Poland, the United States of America, Slovakia, and the Russian Federation. Out of those, 256 (85.6%) and 269 (89.4%) participants from the LUBT010 group and Lucentis group, respectively, completed the study. A higher number of patients discontinued the study in the LUBT010 arm (43 [14.4%]) than in the EU-Lucentis arm (32 [10.6%]). The difference in study discontinuation between study arms is not concerning for CHMP as patients seem to be MAR, and the MNAR assumption was tested via an appropriate tipping point analysis. Of note, the overall discontinuation rate was 12.5% higher than what assumed for sample size planning (7% drop-out rate) and higher than the quality tolerance limit (12% drop-out rate).

Most randomized participants were included in the FAS and the disposition was balanced between treatment arms (295/299 [98.7%] vs. 296/301 [98.3%]). The number of exclusions from the PPS (in total 101 participants, 16.8%) is deemed rather high but may be linked to the 12-month study period and the study discontinuation up to this time. However, the number of patients excluded from the PPS was higher in LUBT010 arm (60 patients [20.1%]) than in the EU-Lucentis arm (41 patients [13.6%]). At Month 3, there were more major protocol deviations in the LUBT010 group than the Lucentis group (18 vs 10) in addition to the higher discontinuation rate (15 vs 11). The major protocol deviations were mostly related to efficacy.

At Month 12 major protocol deviations were still slightly higher in the LUBT010 arm (11.7% [35 out of 299 patients]) compared to the Lucentis arm (8.6% [26 out of 301 patients]). However, the numerical difference is deemed rather small and a major impact on study results was considered unlikely for CHMP.

The distribution of prohibited medications, fellow eye ranibizumab treatment, treatment discontinuation and study discontinuation were compared for the 3-month and 12-month time-point. Only 2 patients received prohibited medication, both in the Lucentis group. The number of patients who received ranibizumab treatment in the fellow eye was similar between groups (2 vs. 7 at Month 3 and 20 vs. 23 at Month 12). The number of patients who discontinued the study treatment was slightly higher in the LUBT010 group compared to the Lucentis group (15 vs. 11 at Month 3 and 45 vs. 36 at Month 12). As most patients who discontinued treatment also discontinued the study similar numbers were seen for study discontinuation (15 vs. 11 at Month 3 and 43 vs. 32 at Month 12).

In summary, the study design, statistical methods and included population are overall deemed adequate for CHMP. Several unclarities regarding study conduct were clarified upon request. However, several major findings and one site-specific critical finding were identified during the EMA routine GCP inspection as outlined below.

The applicant performed 11 routine audits at 10 study sites. In addition to the applicant's conducted audits, 4 study sites were inspected during the conduct of the study (1 EMA inspection for another investigator at site and 3 FDA inspections). Overall, no critical findings were communicated during the audits conducted by the applicant or inspections lead by regulatory agencies. Furthermore, a request for a routine GCP inspection was adopted during the first round of assessment and concerned two study sites, in Country 2 and Country 1 , and at the sponsor's site(s). As per the integrated inspection report, 1 site-specific critical finding and several major findings at the inspected sites and the sponsor's site(s) were identified (see section 2.4.3). The clinical study conducts at the site in Country 1 was considered not compliant with ICH GCP and reported data not trustworthy. In response to that, the applicant performed an impact analysis by excluding the entire data from this study site and updated efficacy, safety and immunogenicity results were provided. It is agreed by CHMP that results upon exclusion of data from the study site in Country 1 are consistent with the initially submitted results and that the newly provided analyses do not impact the study conclusions. It is notable that, despite regular monitoring visits (according to the applicant 1452 interim monitoring visits across 78 sites), GCP non-compliance and instances of metadata manipulation related to IOP measurements at the Country 1 site were seemingly not identified earlier. Considering the conclusion and recommendation from the integrated GCP inspection report, the data obtained from the pivotal Study LRP/LUBT010/2016/008 are acceptable, despite identified major deficiencies. The totality of major findings, as well as unclarities regarding the potential to identify tampering of the blinding solution (see above), are deemed as an uncertainty at clinical level. However, CHMP agreed that the exclusion of data from the GCP non-compliant Bulgarian site does not impact the study conclusions.

Efficacy data and additional analyses

Demographic baseline characteristics appear overall balanced between treatment arms. The median age was 75.0 (range 51-93) and 74.0 (range 52-94) years in the LUBT010 group and Lucentis group, respectively. Roughly half of the study population was enrolled in India and approximately 40% in EU-countries (Poland, Slovakia, Bulgaria, Hungary) but no overview on enrolled participants by country was provided per treatment arm. However, according to the race distribution, only Asian and White patients were represented in the study population, with 158 participants (52.8%) in the LUBT010 arm and 147 participants (48.8%) in the Lucentis arm.

The baseline characteristics of BCVA, iris colour and IOP of the study eye were balanced between treatment arms. The median BCVA by the ETDRS chart was 55.0 (range 22-77) letters in the LUBT010 arm and 54.0 (range 18-76) letters in the Lucentis arm. Generally, the study population is acceptable, while no baseline information regarding the total lesion area and the CNV lesion subtype was seemingly collected (see above). Thus, the homogeneity of the population regarding this ocular parameter remains unclear. Although it is likely that due to randomisation these ocular disease characteristics are comparable between treatment arms, imbalances cannot be excluded.

All randomised participants had at least one noted event in their medical history event, which can be expected based on the study population. The ocular medical history in the study eye was largely comparable between treatment groups. The summarised use of concomitant medication and procedures appears representative of the study population with no major imbalances.

Primary efficacy endpoint

The primary endpoint, **mean change in BCVA from baseline at 12 months**, was met. In the FAS, which was the primary analysis set, the LS mean change from baseline was 11.17 ETDRS letters in the LUBT010

arm and 11.14 ETDRS letters in the Lucentis arm, yielding a difference in the LS means (95% CI) LUBT010 vs Lucentis of 0.03 (-1.82, 1.88). This result was supported by analyses on the PPS where the difference in the LS means (95% CI) was -0.39 (-2.25, 1.46) excluding missing BCVA data and -0.54 (95% CI: -2.44, 1.35) imputing for missing data. Thus, the obtained results are fully contained in the pre-specified bioequivalence margin of ±4 letters as well as within the narrower margin of ±3 letters in both analysis sets.

While the results on mean change in BCVA from baseline at 12 months using the ETDRS letter chart support therapeutic biosimilarity between LUBT010 and Lucentis, the chosen time point is not the most sensitive measure, as mentioned above.

Secondary efficacy endpoints and sensitivity analyses

Secondary efficacy endpoints encompassed mean change in **BCVA from baseline at 3, 6 and 9 month**s, which were comparable between treatment arms.

As outlined earlier, the 3-month time point is deemed of primary interest to demonstrate biosimilarity as regards changes in BCVA. While summarized data on 3-month data were pre-defined in the protocol and provided in the CSR, the applicant provided additional analyses on the treatment difference (95% CI) between LUBT010 and Lucentis upon request.

The LS **mean change in BCVA from baseline at 3 months** was 7.29 ETDRS letters in the LUBT010 arm and 6.82 ETDRS letters in the Lucentis arm in the FAS. This resulted in a LS mean difference (95% CI) of 0.46 (-0.87, 1.79) between LUBT010 and Lucentis. Supportive analysis on the PPS resulted in comparable outcomes (LS mean difference [95% CI] of 0.55 [-0.87, 1.98] between LUBT010 and Lucentis). Furthermore, consistent results were obtained at month 3 in a supportive analysis using a MMRM on the FAS (LS mean difference [95% CI] 0.49 [-0.85, 1.82] between LUBT010 and Lucentis) and the PPS (LS mean difference [95% CI] 0.54 [-0.88, 1.97] between LUBT010 and Lucentis). PPS-based efficacy analyses using the 3-month time point as cut-off, the LS-mean treatment difference between LUBT010 and Lucentis arms was 0.59 (95% CI: -0.77, 1.95) excluding missing BCVA data and 0.32 (95% CI: -1.05, 1.70) imputing for missing BCVA data.

In the primary analysis, missing data were imputed using a MI approach under MAR assumption. The applied tipping point analysis under MNAR assumption showed that the conclusion (95% CI for the difference fell within the pre-specified equivalence margins) would be reversed only if missing values were heavily penalised. Thus, the result was considered robust concerning missing data for primary endpoint change in BCVA after 3 and 12 months. In addition, results were consistent in supportive analyses using a MMRM model. However, as a supplementary analysis to the applied treatment policy approach for intercurrent events, handling using a hypothetical strategy was requested. Using a hypothetical strategy the LS-mean treatment difference between LUBT010 and Lucentis arms was 0.38 (95% CI = -0.96, 1.72) at Month 3 and -0.36 (95% CI = -2.23, 1.51) at Month 12, both results are also within the recommended ±3 letters. A tipping point analysis was applied for all BCVA values imputed and it is agreed that the shift value would need to be far from 0 to change the biosimilarity conclusion.

The 95% CI bounds are well within a margin of ±3 which is seen as margin for a clinically irrelevant difference by the CHMP. The data suggest biosimilarity between LUBT010 and Lucentis at this earlier, more sensitive, time point to assess BCVA changes. In addition, the therapeutic effect was also comparable after **6-months of treatment** (LS mean LUBT010 vs Lucentis [95% CI] 0.91 [-0.75, 2.57] and 0.61 [-1.06, 2.29] in the FAS and PPS, respectively).

Results from the responder analysis based on the proportion of patients with improvement in BCVA by at least 5, 10 and 15 letters, which were requested in the PSM, were consistent with analyses based on mean BCVA changes from baseline.

Exploratory analyses based on the NEI VFQ-25 were additionally provided. The mean NEI VFQ-25 composite score increased gradually in both treatment arms, with no meaningful difference in the mean change from baseline between the biosimilar and the reference medicinal product.

Notably, no subgroup analyses were conducted. Although of interest, this was not seen as highly critical for a biosimilarity exercise by the CHMP as it is not expected that larger differences between biosimilar and originator occur in certain subgroups defined by baseline characteristics. However, the applicant presented the impact of the post-baseline event ADA-status on the primary efficacy endpoint. There was a total of 40 patients who tested positive for treatment-emergent ADA at 12 months (LUBT010, n=19; Lucentis, n=21) and 482 patients who tested negative (LUBT010, n=234; Lucentis, n=248). For the ADA positive sub-group, the LS-mean treatment difference between LUBT010 and Lucentis arms was 3.70 with 95% CI (-3.54, 10.93). For the ADA negative sub-group, the LS-mean treatment difference between LUBT010 and Lucentis arms was 0.04 with 95% CI (-1.86, 1.94). A different impact of ADAs on the mean change in BCVA from baseline at 12 months cannot be ruled out but, if at all, seems to positively impact the outcome.

5.3.2.3. Conclusions on the clinical efficacy

The therapeutic biosimilarity was solely based on BCVA, as no anatomical endpoints were evaluated in the pivotal study LRP/LUBT010/2016/008; this remains an uncertainty.

Missing information on ocular baseline characteristics and major deficiencies identified during a GCP routine inspection posed further uncertainties for biosimilarity at clinical level. However, the critical GCP finding identified was considered a site-specific, isolated case without major impact on the efficacy results, following exclusion of data from the non-compliant site, where only 7 patients had been enrolled.

Overall, the CHMP concluded that the results on the change in BCVA from baseline are sufficient to support the therapeutic biosimilarity between LUBT010 and EU-Lucentis. In addition, it was noted that, in the pivotal trial, the primary efficacy results are supported by the secondary efficacy endpoints. Therefore, despite the above-mentioned remaining uncertainties, biosimilarity on efficacy between LUBT010 and EU-Lucentis can be concluded.

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – (ADR)' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

Study LRP/LUBT010/2022/001

The safety of LUBT010 and Lucentis was comparatively assessed by monitoring treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), physical examination, vital signs measurements, 12-lead ECG, clinical laboratory evaluations and ophthalmic assessments.

All AEs occurring after the signing of the informed consent were to be documented and recorded. Events that occurred prior to the start of study drug administration were considered "Non-Treatment-Emergent" AEs, and those that occurred after the start of the first administration of study drug, were considered TEAEs. Patients were instructed at the beginning of the study to inform the Investigator or during every clinic visit for any adverse effects experienced since the last visit.

Treatment-emergent adverse events are defined as AEs that begin after administration of any study treatment or if they started prior to study drug administration but worsened after dosing, given that worsening started within a treatment period. All TEAEs were summarized by SOC, PT (using the MedDRA version 27.0.), and treatment as the number and percentage of patients experiencing the AE and the number of episodes reported. A patient was only counted once per SOC and PT within a treatment and overall. Intensity or severity of AEs, including laboratory findings, were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0. If a patient had multiple events occurring in the same SOC or same PT, then the event with the highest severity/grade was used in summary analyses. All AEs classified as Grade 4 or Grade 5 and some in Grade 3 (based on medical and clinical judgment) were to be reported as an SAE.

Vital signs were measured at pre and post treatment on drug administration days and consisted of (systolic/diastolic blood pressure, body temperature, pulse rate, and respiratory rate). Vital signs and change from baseline values were summarized by treatment and visit using descriptive statistics (N, mean, SD, median, Min, and Max).

Electrocardiograms were conducted at the Screening and V10 (EOS)/Early discontinuation. Individual electrocardiograms were listed by parameter and visit.

Physical examinations were conducted at the Screening visit, on Day -1 (check-in) and Day 2 (check-out) of each treatment period, and at the V10 (EOS)/Early discontinuation. Any abnormal physical examination findings were to be summarized at baseline and as a shift from baseline to V10 (EOS)/Early discontinuation.

Study LRP/LUBT010/2016/008

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

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

Signs and symptoms clearly associated with the disease under study (including symptoms of disease progression) were to be reported as AEs if they were 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 considered deterioration of disease-related signs and symptoms to be caused directly by the study drug.

Abnormal laboratory values/ electrocardiograms/ vital signs/ ophthalmic/ physical & systemic examination were to be reported as AEs only if the Investigator considered 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 exceeded the dose prescribed to the patient had, 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 was to 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.

5.4.2. Patient exposure

Study LRP/LUBT010/2022/001

Patient exposure

All participants that receive at least one dose of investigational medicinal product were included in the SAF and were analysed according to the actual treatment received (N = 20). All received 3 injections.

Demographics and baseline characteristics

The demographics and baseline characteristics of study LRP/LUBT010/2022/001 are described in section 5.2.2.4. *Bioequivalence.*

Study LRP/LUBT010/2016/008

Patient exposure

The Safety Analysis Set included all patients who receive at least one dose of study medication. The participant flow of study LRP/LUBT010/2016/008 is described in section 5.3.2.1.4.

Demographics and baseline characteristics

The demographics and baseline characteristics of study LRP/LUBT010/2016/008 are described in section 5.3.2.1.4.

5.4.3. Adverse events

All serious and non-serious AEs were coded according to the MedDRA Version 27.0 (Study LRP/LUBT010/2022/001) and Version 26.0 (LRP/LUBT010/2016/008).

5.4.3.1. Adverse drug reactions

Adverse events and drug reactions in study LRP/LUBT010/2022/001

Summary of Adverse Events

Overall, 6 AEs (three per arm) were reported, all them were considered TEAEs. In the LUBT010 arm, two TEAEs were considered mild and one moderate. In the Lucentis arm, two TEAEs were considered mild and one severe. All TEAEs were considered non-related to the drug. Only one subject in the Lucentis arm had a SAEs, non-related to the drug. None of the AEs led to treatment discontinuation.

In terms of TEAEs by SOC and PT, the following events were noted:

- LUBT010 arm: vertigo, cataract, viral infection, blood glucose increased, back pain, and hypertension.
- Lucentis arm: vitreous floaters, femur fracture, and haematoma.

Adverse events and drug reactions in study LRP/LUBT010/2016/008

Summary of Adverse Events

A total of 319 (53.2%) patients experienced at least 1 TEAE during the study, including 156 (52.2%) patients in the LUBT010 arm and 163 (54.2%) patients in the Lucentis arm. A majority of the patients reported TEAEs that were not related to the study drug (307 [51.2%] patients overall, including 149 [49.8%] patients in the LUBT010 arm and 158 [52.5%] patients in the Lucentis arm).

Overall, 48 (8.0%) patients reported Treatment-Emerging Serious Adverse Events (TESAEs), with 25 (8.4%) patients in the LUBT010 arm and 23 (7.6%) patients in the Lucentis arm. Of these, drug-related TESAEs were reported by 3 (0.5%) patients overall (1 [0.3%] patient in the LUBT010 arm and 2 [0.7%] patients in the Lucentis arm).

Overall, 7 (1.2%) patients died in the study due to TEAE (3 [1.0%] patients in the LUBT010 arm and 4 [1.3%] patients in the Lucentis arm). None of the TEAEs leading to death were assessed as drug-related.

A total of 12 (2.0%) patients experienced at least 1 TEAE leading to discontinuation of study drug, including 6 (2.0%) patients each, in the LUBT010 and Lucentis arms. Ocular TEAEs in the study eye leading to study drug discontinuation was reported by 7 (1.2%) patients overall, including 2 (0.7%) patients in the LUBT010 arm and 5 (1.7%) patients in the Lucentis arm. A total of 4 (0.7%) patients experienced at least 1 non-ocular TEAE leading to study drug discontinuation, including 3 (1.0%) patients in the LUBT010 arm and 1 (0.3%) patient in the Lucentis arm.

Table 32: Summary of all adverse events (SAS)

Number of Patients	LUBT010 (N=299) n (%)	Lucentis® (N=301) n (%)	Total (N=600) n (%)
Adverse Events	160 (53.5)	168 (55.8)	328 (54.7)
Treatment Emergent Adverse Events (TEAEs)	**156 (52.2)**	**163 (54.2)**	**319 (53.2)**
TEAE Severity			
Mild	68 (22.7)	73 (24.3)	141 (23.5)
Moderate	67 (22.4)	66 (21.9)	133 (22.2)
Severe	15 (5.0)	17 (5.6)	32 (5.3)
Life-threatening	3 (1.0)	3 (1.0)	6 (1.0)
Fatal	3 (1.0)	4 (1.3)	7 (1.2)
TEAE Causality			
Related	7 (2.3)	5 (1.7)	12 (2.0)
Related	4 (1.3)	2 (0.7)	6 (1.0)
Possibly Related	3 (1.0)	3 (1.0)	6 (1.0)
Not Related	149 (49.8)	158 (52.5)	307 (51.2)
Unlikely Related	20 (6.7)	19 (6.3)	39 (6.5)
Not Related	129 (43.1)	139 (46.2)	268 (44.7)
Ocular TEAEs in the study eye	**54 (18.1)**	**58 (19.3)**	**112 (18.7)**
TEAE Severity			
Mild	40 (13.4)	39 (13.0)	79 (13.2)
Moderate	12 (4.0)	13 (4.3)	25 (4.2)
Severe	2 (0.7)	6 (2.0)	8 (1.3)
Life-threatening	0	0	0
Fatal	0	0	0
TEAE Causality			
Related	7 (2.3)	4 (1.3)	11 (1.8)
Related	4 (1.3)	2 (0.7)	6 (1.0)
Possibly Related	3 (1.0)	2 (0.7)	5 (0.8)
Not Related	47 (15.7)	54 (17.9)	101 (16.8)
Unlikely Related	3 (1.0)	6 (2.0)	9 (1.5)

Not Related	44 (14.7)	48 (15.9)	92 (15.3)
Ocular TEAEs in the non-study eye	**37 (12.4)**	**36 (12.0)**	**73 (12.2)**
TEAE Severity			
Mild	20 (6.7)	19 (6.3)	39 (6.5)
Moderate	16 (5.4)	17 (5.6)	33 (5.5)
Severe	1 (0.3)	0	1 (0.2)
Life-threatening	0	0	0
Fatal	0	0	0
TEAE Causality			
Related	0	0	0
Not Related	37 (12.4)	36 (12.0)	73 (12.2)
Unlikely Related	0	4 (1.3)	4 (0.7)
Not Related	37 (12.4)	32 (10.6)	69 (11.5)
Non-Ocular TEAEs	**118 (39.5)**	**116 (38.5)**	**234 (39.0)**
TEAE Severity			
Mild	53 (17.7)	54 (17.9)	107 (17.8)
Moderate	47 (15.7)	44 (14.6)	91 (15.2)
Severe	12 (4.0)	11 (3.7)	23 (3.8)
Life-threatening	3 (1.0)	3 (1.0)	6 (1.0)
Fatal	3 (1.0)	4 (1.3)	7 (1.2)
TEAE Causality			
Related	0	1 (0.3)	1 (0.2)
Related	0	0	0
Possibly Related	0	1 (0.3)	1 (0.2)
Not Related	118 (39.5)	115 (38.2)	233 (38.8)
Unlikely Related	19 (6.4)	12 (4.0)	31 (5.2)
Not Related	99 (33.1)	103 (34.2)	202 (33.7)
TEAEs leading to IP discontinuation	**6 (2.0)**	**6 (2.0)**	**12 (2.0)**
Ocular TEAEs in the study eye leading to IP discontinuation	2 (0.7)	5 (1.7)	7 (1.2)
Ocular TEAEs in the non-study eye leading to IP discontinuation	1 (0.3)	0	1 (0.2)
Non-ocular TEAEs leading to IP discontinuation	3 (1.0)	1 (0.3)	4 (0.7)
Serious Adverse Events (SAEs)	**26 (8.7)**	**23 (7.6)**	**49 (8.2)**
Ocular SAEs in the study Eye	2 (0.7)	5 (1.7)	7 (1.2)

Number of Patients	LUBT010 (N=299) n (%)	Lucentis® (N=301) n (%)	Total (N=600) n (%)
Ocular SAEs in the non-study Eye	1 (0.3)	0	1 (0.2)
Non-ocular SAEs	23 (7.7)	18 (6.0)	41 (6.8)
TESAEs	**25 (8.4)**	**23 (7.6)**	**48 (8.0)**
SAE Causality			
Related	1 (0.3)	2 (0.7)	3 (0.5)
Not Related	24 (8.0)	21 (7.0)	45 (7.5)
Ocular TESAEs in the study eye	2 (0.7)	5 (1.7)	7 (1.2)
SAE Causality			
Related	1 (0.3)	2 (0.7)	3 (0.5)
Not Related	1 (0.3)	3 (1.0)	4 (0.7)
Ocular TESAEs in the non-study Eye	1 (0.3)	0	1 (0.2)
SAE Causality			
Related	0	0	0
Not Related	1 (0.3)	0	1 (0.2)
Non-ocular TESAEs	22 (7.4)	18 (6.0)	40 (6.7)
SAE Causality			
Related	0	0	0
Not Related	22 (7.4)	18 (6.0)	40 (6.7)
TEAEs leading to death	3 (1.0)	4 (1.3)	7 (1.2)

Abbreviations: AE=adverse event, SAE=serious adverse event, TEAE=treatment-emergent adverse event, TESAE=serious TEAE.
N is the number of patients in the Safety Analysis Set.
n is the number of patients in each category.
Percentages were calculated based on N.
Treatment-emergent adverse events were defined as any adverse event that began or worsened in severity after at least one dose of study drug had been administered.
Adverse event was classified as treatment-emergent in the case where it was not possible to define an AE as treatment-emergent or not.
A "Related" TEAE was defined as a TEAE with a relationship to study drug as "Related" or "Possibly Related" to study drug. A "Not Related" TEAE was defined as a TEAE non-related to study drug as "Unlikely Related" or "Not Related".
If a patient had >1 AE, they were counted only once in the patients count for the relevant row of the table.

Treatment-emergent adverse events by severity

Severe TEAEs were reported by 32 (5.3%) patients. In the LUBT010 arm, severe TEAEs were reported by a total of 15 (5.0%) patients. In the Lucentis arm, severe TEAEs were reported by a total of 17 (5.6%) patients, where 2 TEAEs were assessed as related to study drug: endophthalmitis and non-infectious endophthalmitis (also led to study drug discontinuation).

Table 33: Severe and life-threatening treatment-emergent adverse events (SAS)

System Organ Class Preferred Term	Treatment at Onset of Adverse Event			
	Severity	Lupin Ranibizumab (N = 299) n (%)	Lucentis® (N = 301) n (%)	Overall (N = 600) n (%)
Any TEAE	Mild	68(22.7)	73(24.3)	141(23.5)
	Moderate	67(22.4)	66(21.9)	133(22.2)
	Severe	15(5.0)	17(5.6)	32 (5.3)
	Life-Threatening	3(1.0)	3(1.0)	6(1.0)
	Death	3(1.0)	4(1.3)	7(1.2)
Blood and lymphatic system disorders	**Severe**	**2 (0.7)**	**1 (0.3)**	**3 (0.5)**
	Life-threatening	**0**	**0**	**0**
Iron deficiency anaemia	Severe	2 (0.7)	0	2 (0.3)
Normocytic anaemia	Severe	0	1 (0.3)	1 (0.2)
Cardiac disorders	**Severe**	**4 (1.3)**	**2 (0.7)**	**6 (1.0)**
	Life-threatening	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Atrial fibrillation	Severe	1 (0.3)	1 (0.3)	2 (0.3)
Myocardial infarction	Severe	1 (0.3)	0	1 (0.2)
Acute myocardial infarction	Life-threatening	0	1 (0.3)	1 (0.2)
Atrioventricular block complete	Severe	1 (0.3)	0	1 (0.2)
Atrioventricular block second degree	Severe	1 (0.3)	0	1 (0.2)
Cardiac failure	Severe	0	1 (0.3)	1 (0.2)
Supraventricular tachycardia	Life-threatening	1 (0.3)	0	1 (0.2)
Eye disorders	**Severe**	**2 (0.7)**	**4 (1.3)**	**6 (1.0)**
Neovascular age-related macular degeneration	Severe	1 (0.3)	0	1 (0.2)
Cataract	Severe	1 (0.3)	0	1 (0.2)
Retinal haemorrhage	Severe	0	2 (0.7)	2 (0.3)
Non-infectious endophthalmitis	Severe	0	1 (0.3)	1 (0.2)
Retinal detachment	Severe	0	1 (0.3)	1 (0.2)
Gastrointestinal disorders	**Severe**	**1 (0.3)**	**0**	**1 (0.2)**
Ulcerative gastritis	Severe	1 (0.3)	0	1 (0.2)
Infections and infestations	**Severe**	**0**	**1 (0.3)**	**1 (0.2)**
Pneumonia	Severe	0	1 (0.3)	1 (0.2)
Endophthalmitis	Severe	0	1 (0.3)	1 (0.2)
Injury, poisoning and procedural complications	**Severe**	**1 (0.3)**	**5 (1.7)**	**6 (1.0)**
Cataract traumatic	Severe	0	1(0.3)	1 (0.2)
Comminuted fracture	Severe	0	1 (0.3)	1 (0.2)
Humerus fracture	Severe	0	1 (0.3)	1 (0.2)
Lower limb fracture	Severe	1 (0.3)	0	1 (0.2)
Post procedural complication	Severe	0	1 (0.3)	1 (0.2)
Rib fracture	Severe	0	1 (0.3)	1 (0.2)
Investigations	**Severe**	**2 (0.7)**	**0**	**2 (0.3)**
Intraocular pressure increased	Severe	1 (0.3)	0	1 (0.2)
Blood creatinine increased	Severe	1 (0.3)	0	1 (0.2)
Metabolism and nutrition disorders	**Severe**	**0**	**1 (0.3)**	**1 (0.2)**
Hyponatraemia	Severe	0	1 (0.3)	1 (0.2)

Musculoskeletal and connective tissue disorders	**Severe**	**0**	**1 (0.3)**	**1 (0.2)**
Spinal osteoarthritis	Severe	0	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Severe**	**0**	**1 (0.3)**	**1 (0.2)**
	Life-threatening	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Lung cancer metastatic	Life-threatening	1 (0.3)	0	1 (0.2)
Prostate cancer	Life-threatening	0	1 (0.3)	1 (0.2)
Rectal adenocarcinoma	Severe	0	1 (0.3)	1 (0.2)
Nervous system disorders	**Severe**	**3 (1.0)**	**0**	**3 (1.0)**
	Life-threatening	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Headache	Severe	1 (0.3)	0	1 (0.2)
Dizziness	Life-threatening	0	1 (0.3)	1 (0.2)
Syncope	Severe	1 (0.3)	0	1 (0.2)
	Life-threatening	1 (0.3)	0	1 (0.2)
Ischaemic stroke	Severe	1 (0.3)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**Severe**	**0**	**2 (0.7)**	**2 (0.3)**
Laryngeal oedema	Severe	0	1 (0.3)	1 (0.2)
Laryngeal stenosis	Severe	0	1 (0.3)	1 (0.2)
Vascular disorders	**Severe**	**2 (0.7)**	**0**	**2 (0.3)**
	Life-threatening	**1 (0.3)**	**0**	**1 (0.2)**
Hypertension	Severe	1 (0.3)	0	1 (0.2)
	Life-threatening	1 (0.3)	0	1 (0.2)
Orthostatic hypotension	Severe	1 (0.3)	0	1 (0.2)

Abbreviations: N = number of patients; n = number of patients in the category; TEAE = treatment-emergent adverse event.
Notes: Percentage was calculated based on the number of patients treated as the denominator.
Dictionary: MedDRA version 26.0

Ocular Treatment-Emergent Adverse Events

In the study eye, 112 (18.7%) patients experienced at least one ocular TEAE (LUBT010 arm 54 [18.1%] and the Lucentis arm 58 [19.3%]). In the non-study eye, 73 [12.2%] patients had at least one ocular TEAE (LUBT010 arm 37 [12.4%]) and the Lucentis arm (36 [12.0%].

Table 34: Incidence of ocular TEAEs occurring in ⩾2 patients in either treatment arm (SAS)

Adverse Event	Lupin Ranibizumab (N=299)	Lucentis® (N=301)
Study Eye		
Any Ocular Treatment-Emergent Adverse Event	54 (18.1%)	58 (19.3%)
Eye disorders	47 (15.7%)	48 (15.9%)
Conjunctival haemorrhage	10 (3.3%)	14 (4.7%)
Cataract	2 (0.7%)	8 (2.7%)
Dry eye	7 (2.3%)	1 (0.3%)
Eye pain	3 (1.0%)	5 (1.7%)
Neovascular age-related macular degeneration	4 (1.3%)	4 (1.3%)
Ocular hyperaemia	1 (0.3%)	4 (1.3%)
Ocular hypertension	3 (1.0%)	1 (0.3%)
Punctate keratitis	3 (1.0%)	1 (0.3%)
Vitreous floaters	2 (0.7%)	2 (0.7%)
Foreign body sensation in eyes	1 (0.3%)	2 (0.7%)
Posterior capsule opacification	1 (0.3%)	2 (0.7%)
Retinal haemorrhage	1 (0.3%)	2 (0.7%)
Retinal degeneration	0	2 (0.7%)
Vision blurred	0	2 (0.7%)

Infections and Infestations	5 (1.7%)	7(2.3%)
Conjunctivitis	4 (1.3%)	5 (1.7%)
Endophthalmitis	1 (0.3%)	1 (0.3%)
Investigations	4 (1.3%)	2 (0.7%)
Intraocular pressure increased	4 (1.3%)	2 (0.7%)
Non-Study Eye		
Any Ocular Treatment-Emergent Adverse Event	37 (12.4%)	36 (12.0%)
Eye disorders	36 (12.0%)	34 (11.3%)
Neovascular age-related macular degeneration	19 (6.4%)	24 (8.0%)
Cataract	3 (1.0%)	5 (1.7%)
Posterior capsule opacification	4 (1.3%)	1 (0.3%)
Dry age-related macular degeneration	2 (0.7%)	2 (0.7%)
Dry eye	3 (1.0%)	1 (0.3%)
Punctate keratitis	2 (0.7%)	1 (0.3%)
Conjunctival haemorrhage	2 (0.7%)	0

Abbreviations: TEAE= treatment-emergent adverse event, MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, SOC=system organ class.
N is the number of patients in the Safety Analysis Set.
n is the number of patients in each category.
Percentages were calculated based on N.
Patients experiencing multiple events within the same SOC and PT were counted only once under those categories.
Adverse event terms were coded using MedDRA version 26.0.

Incidence of Ocular Treatment-Emergent Adverse Events by Severity

Overall, a majority of the patients reported ocular TEAEs in the study eye that were of mild (79 [13.2%] patients) or moderate (25 [4.2%] patients) intensity, while severe TEAEs were reported by 8 (1.3%) patients. Severe ocular TEAE in the non-study eye was reported by 1 (0.3%) patient in the LUBT010 arm, assessed as not related to study drug, and led to study drug discontinuation: neovascular age-related macular degeneration.

Incidence of Ocular Treatment-Emergent Adverse Events by Relationship to Study Drug

Table 35: Incidence of ocular, study drug-related TEAEs (SAS)

Number of Patients	LUBT010 (N=299) n (%)	Lucentis® (N=301) n (%)	Total (N=600) n (%)
Study eye			
Any Ocular, Study Drug-related TEAE in study eye	7 (2.3)	4 (1.3)	11 (1.8)
Eye disorders	5 (1.7)	2 (0.7)	7 (1.2)
Eye pain	1 (0.3)	0	1 (0.2)
Ocular hypertension	1 (0.3)	0	1 (0.2)
Macular hole	1 (0.3)	0	1 (0.2)
Uveitis	1 (0.3)	0	1 (0.2)
Vitreous opacities	1 (0.3)	0	1 (0.2)
Anterior chamber inflammation	0	1 (0.3)	1 (0.2)
Iridocyclitis	0	1 (0.3)	1 (0.2)
Non-infectious endophthalmitis	0	1 (0.3)	1 (0.2)

Infections and infestations	0	1 (0.3)	1 (0.2)
Endophthalmitis	0	1 (0.3)	1 (0.2)
Investigations	2 (0.7)	1 (0.3)	3 (0.5)
Intraocular pressure increased	2 (0.7)	1 (0.3)	3 (0.5)
Non-study eye			
Any Ocular, Study Drug-related TEAE in the non-study eye	0	0	0

Abbreviations: TEAE= treatment-emergent adverse event, MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, SOC=system organ class.
N is the number of patients in the Safety Analysis Set. n is the number of patients in each category. Percentages were calculated based on N.
Patients experiencing multiple events within the same SOC and PT were counted only once under those categories.
Adverse event terms were coded using MedDRA version 26.0.

No ocular TEAEs occurring in the non-study eye were assessed as related to the study drug in either arm.

Non-ocular TEAEs

At least 1 non-ocular TEAE was reported in 234 [39.0%] patients overall, including 118 [39.5%] patients in the LUBT010 arm and 116 [38.5%] patients in the Lucentis arm. Overall, the most commonly reported non-ocular TEAEs at the SOC level were infections and infestations (88 [14.7%] patients overall) and metabolism and nutrition disorders (40 [6.7%] patients overall).

Table 36: Incidence of non-ocular TEAEs occurring in ⩾2 patients in either treatment arm (SAS)

Number of Patients	LUBT010 (N=299) n (%)	Lucentis® (N=301) n (%)	Total (N=600) n (%)
Any Non-Ocular Treatment-Emergent Adverse Event	118 (39.5)	116 (38.5)	234 (39.0)
Blood and lymphatic system disorders	7 (2.3)	5 (1.7)	12 (2.0)
Anaemia	2 (0.7)	3 (1.0)	5 (0.8)
Iron deficiency anaemia	2 (0.7)	0	2 (0.3)
Thrombocytopenia	2 (0.7)	0	2 (0.3)
Cardiac disorders	12 (4.0)	10 (3.3)	22 (3.7)
Atrial fibrillation	3 (1.0)	3 (1.0)	6 (1.0)
Myocardial infarction	2 (0.7)	1 (0.3)	3 (0.5)
Ear and labyrinth disorders	1 (0.3)	3 (1.0)	4 (0.7)
Vertigo	0	3 (1.0)	3 (0.5)
Gastrointestinal disorders	12 (4.0)	13 (4.3)	25 (4.2)
Diarrhoea	4 (1.3)	4 (1.3)	8 (1.3)
Abdominal pain upper	1 (0.3)	2 (0.7)	3 (0.5)
Vomiting	1 (0.3)	2 (0.7)	3 (0.5)
Diverticulum intestinal	0	2 (0.7)	2 (0.3)

Number of Patients	LUBT010 (N=299) n (%)	Lucentis® (N=301) n (%)	Total (N=600) n (%)
Gastrooesophageal reflux disease	0	2 (0.7)	2 (0.3)
General disorders and administration site conditions	8 (2.7)	15 (5.0)	23 (3.8)
Pyrexia	7 (2.3)	11 (3.7)	18 (3.0)
Hyperthermia	0	2 (0.7)	2 (0.3)
Oedema peripheral	0	2 (0.7)	2 (0.3)
Immune system disorders	2 (0.7)	3 (1.0)	5 (0.8)
Drug hypersensitivity	1 (0.3)	2 (0.7)	3 (0.5)
Infections and infestations	41 (13.7)	47 (15.6)	88 (14.7)
Nasopharyngitis	5 (1.7)	11 (3.7)	16 (2.7)
Urinary tract infection	10 (3.3)	6 (2.0)	16 (2.7)
COVID-19	10 (3.3)	5 (1.7)	15 (2.5)
Influenza	3 (1.0)	5 (1.7)	8 (1.3)
Upper respiratory tract infection	3 (1.0)	5 (1.7)	8 (1.3)
Bronchitis	2 (0.7)	2 (0.7)	4 (0.7)
Pneumonia	1 (0.3)	2 (0.7)	3 (0.5)
Respiratory tract infection	1 (0.3)	2 (0.7)	3 (0.5)
Respiratory tract infection viral	1 (0.3)	2 (0.7)	3 (0.5)
Injury, poisoning and procedural complications	10 (3.3)	10 (3.3)	20 (3.3)
Fall	4 (1.3)	4 (1.3)	8 (1.3)
Skin abrasion	2 (0.7)	0	2 (0.3)
Investigations	8 (2.7)	12 (4.0)	20 (3.3)
Blood glucose increased	3 (1.0)	4 (1.3)	7 (1.2)
Blood creatinine increased	2 (0.7)	1 (0.3)	3 (0.5)
Blood pressure increased	2 (0.7)	1 (0.3)	3 (0.5)
Metabolism and nutrition disorders	15 (5.0)	25 (8.3)	40 (6.7)
Diabetes mellitus	6 (2.0)	14 (4.7)	20 (3.3)
Type 2 diabetes mellitus	2 (0.7)	2 (0.7)	4 (0.7)
Gout	1 (0.3)	2 (0.7)	3 (0.5)
Hyperglycaemia	1 (0.3)	2 (0.7)	3 (0.5)
Hyperlipidaemia	2 (0.7)	1 (0.3)	3 (0.5)
Hyperuricaemia	1 (0.3)	2 (0.7)	3 (0.5)
Musculoskeletal and connective tissue disorders	9 (3.0)	9 (3.0)	18 (3.0)
Osteoarthritis	3 (1.0)	3 (1.0)	6 (1.0)
Arthralgia	2 (0.7)	1 (0.3)	3 (0.5)

Number of Patients	LUBT010 (N=299) n (%)	Lucentis® (N=301) n (%)	Total (N=600) n (%)
Back pain	1 (0.3)	2 (0.7)	3 (0.5)
Pain in extremity	2 (0.7)	0	2 (0.3)
Spinal pain	2 (0.7)	0	2 (0.3)
Nervous system disorders	12 (4.0)	15 (5.0)	27 (4.5)
Headache	3 (1.0)	4 (1.3)	7 (1.2)
Dizziness	0	3 (1.0)	3 (0.5)
Syncope	3 (1.0)	0	3 (0.5)
Myelopathy	0	2 (0.7)	2 (0.3)
Renal and urinary disorders	6 (2.0)	10 (3.3)	16 (2.7)
Nephrolithiasis	0	2 (0.7)	2 (0.3)
Renal cyst	0	2 (0.7)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	9 (3.0)	9 (3.0)	18 (3.0)
Cough	6 (2.0)	3 (1.0)	9 (1.5)
Epistaxis	2 (0.7)	0	2 (0.3)
Vascular disorders	12 (4.0)	12 (4.0)	24 (4.0)
Hypertension	8 (2.7)	11 (3.7)	19 (3.2)
Orthostatic hypotension	2 (0.7)	0	2 (0.3)

Abbreviations: COVID-19=coronavirus disease 2019, TEAE=treatment-emergent adverse event, MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, SOC=system organ class.
N is the number of patients in the Safety Analysis Set. n is the number of patients in each category. Percentages were calculated based on N.
Patients experiencing multiple events within the same SOC and PT were counted only once under those categories.
Adverse event terms were coded using MedDRA version 26.0.

Incidence of Non-ocular Treatment-Emergent Adverse Events by severity

Overall, a majority of the patients reported non-ocular TEAEs that were of mild (107 [17.8%] patients)

or moderate (91 [15.2%] patients) intensity, while severe TEAEs were reported by 23 (3.8%) patients. A total of 6 (1.0%) patients reported life-threatening non-ocular TEAEs, while 7 (1.2%) patients reported fatal non-ocular TEAEs. Of note, with regards to the fatal non-ocular deaths, these occurred in 3 [1.0%] patients in the LUBT010 arm and in 4 [1.3%] patients in the Lucentis arm. Thus, TEAEs that led to death were comparable between treatment arms and, as detailed thereafter in this AR, none were judged as related to the study drug.

No ocular event led to death.

In the LUBT010 arm, a majority of the patients reported non-ocular TEAEs that were of mild (53 [17.7%] patients) or moderate (47 [15.7%] patients) intensity. Severe non-ocular TEAEs were reported by a total of 12 (4.0%) patients, and all were not related to study drug.

In the Lucentis arm, a majority of the patients reported non-ocular TEAEs that were of mild (54 [17.9%] patients) or moderate (44 [14.6%] patients) intensity. Severe TEAEs were reported by a total of 11 (3.7%) patients, where all were not related to study drug.

Incidence of Non-ocular Treatment-Emergent Adverse Events by Relationship to Study Drug

At the PT level, 1 (0.2%) patient overall, and from the Lucentis arm reported non-ocular TEAEs of vertigo and cerebral ischaemia, that were assessed as related to the study drug.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Study LRP/LUBT010/2022/001

Serious adverse events: One SAE was reported by 1 (5.0%) patient in the Lucentis treatment arm (Femur fracture).

Deaths: No deaths were reported during this study.

Other significant events were not reported in this study.

Study LRP/LUBT010/2016/008

Serious adverse events

Incidence of Ocular, Treatment-Emergent, Serious Adverse Events

Overall, 7 (1.2%) patients reported ocular TESAEs in the study eye (2 [0.7%] patients in the LUBT010 arm and 5 [1.7%] patients in the Lucentis arm).

In the LUBT010 arm, 2 patients experienced ocular TESAEs in the study eye: macular hole (assessed as possibly related to study drug) and endophthalmitis (assessed as not related to study drug).

In the Lucentis arm, 5 patients experienced ocular TESAEs in the study eye: non-infectious endophthalmitis, endophthalmitis, retinal detachment, retinal haemorrhage, and cataract traumatic. Out of these, the TESAEs of non-infectious endophthalmitis and endophthalmitis were assessed as possibly related to study drug whereas, the rest (retinal detachment, retinal haemorrhage, and cataract traumatic) were assessed as not related to study drug.

One (0.2%) patient in LUBT010 arm experienced ocular TESAEs in the non-study eye, i.e., nAMD (assessed as not related to study drug). No ocular TESAEs were reported in the non-study eye in the Lucentis arm.

Incidence of Non-ocular, Treatment-Emergent, Serious Adverse Events

The most common non-ocular TESAEs by SOC were cardiac disorders (12 [2.0%] patients), injury, poisoning and procedural complications (6 [1.0%] patients), and nervous system disorders (5 [0.8%] patients). The most common non-ocular TESAEs by PT included myocardial infarction (3 [0.5%] patients), atrial fibrillation and syncope (2 [0.3%] patients, each). All other non-ocular TESAEs by PT were reported in 1 patient, each.

In the LUBT010 arm, the most common non-ocular TESAEs by SOC were cardiac disorders (7 [2.3%] patients), nervous system disorders (4 [1.3%] patients), gastrointestinal disorders and vascular disorders (3 [1.0%] patients, each).

In the Lucentis arm, the most common non-ocular TESAEs by SOC were cardiac disorders and injury, poisoning and procedural complications (5 [1.7%] patients, each), neoplasms benign, malignant and unspecified (incl. cysts and polyps) and infections and infestations (3 [1.0%] patients, each).

Deaths

A total of 7 (1.2%) patients reported TEAEs that led to death (3 [1.0%] patients in the LUBT010 arm and 4 [1.3%] patients in the Lucentis arm). None of the TEAEs leading to death were assessed as drug-related. In addition, no ocular event led to death.

Other significant events

No other significant events, such as AEs of special interest were pre-defined and reported for this study.

5.4.5. Discontinuation due to adverse events

Study LRP/LUBT010/2022/001

No discontinuations were reported.

Study LRP/LUBT010/2016/008

A total of 12 (2.0%) patients reported TEAEs that led to discontinuation of study drug (6 [2.0%] patients in each treatment arm).

Incidence of Ocular, Treatment-Emergent Adverse Events Leading to Discontinuation of the Study Drug

In LUBT010 arm, 2 patients experienced ocular TEAEs in the study eye that led to discontinuation of study drug: macular hole (assessed as possibly related to study drug) and endophthalmitis (assessed as not related to study drug).

In the Lucentis arm, 5 patients experienced ocular TEAEs in the study eye (non-infectious endophthalmitis, endophthalmitis, retinal degeneration, retinal detachment, and retinal haemorrhage). Out of these, the ocular TEAEs of non-infectious endophthalmitis and endophthalmitis were assessed as related to study drug whereas, the rest (retinal degeneration, retinal detachment, and retinal haemorrhage) were assessed as not related to study drug. Additionally, all ocular TEAEs that led to discontinuation of study drug were serious TEAEs except retinal degeneration. One (0.2%) patient in the LUBT010 arm experienced ocular TEAEs in the non-study eye that led to discontinuation of study drug: nAMD (TESAE assessed as not related to study drug). No ocular TEAEs that led to discontinuation of study drug were reported in the non-study eye in the Lucentis arm.

Incidence of Non-ocular, Treatment-Emergent Adverse Events Leading to Discontinuation of the Study Drug

Overall, 4 (0.7%) patients reported non-ocular TEAEs that led to discontinuation of study drug (3 [1.0%] patients in the LUBT010 arm and 1 [0.3%] patient in the Lucentis arm).

In the LUBT010 arm, 3 patients experienced non-ocular TEAEs that led to discontinuation of study drug: supraventricular tachycardia, lung cancer metastatic, syncope, and hypertension.

All TEAEs were serious, and none were assessed by the Investigator as related to the study drug.

In the Lucentis arm, 1 patient reported non-ocular TEAE of COVID-19 leading to discontinuation of study drug. The TEAE was serious and assessed as not related to the study drug.

5.4.6. Immunological events

Please refer to section 5.2.3.5. *Immunological events*.

5.4.7. Safety related to drug-drug interactions and other interactions

Not applicable.

5.4.8. Vital signs and laboratory findings

LRP/LUBT010/2022/001

Clinical Laboratory Evaluation

Samples for hematology, biochemistry, urinalysis were collected at the screening visit and visit 10 (end of study) or whenever a patients discontinued early from study. Vital signs (including body temperature, pulse rate, blood pressure, and respiratory rate) were measured at before and after treatment on the days of drug administration. 12-Lead ECG was assessed at the screening visit and at EOS visit. Urin pregnancy tests, physcial examinations and ophthalmic examinations were conducted at baseline (visit 1), visit 5, visit 6 and EOS.

There were no clinically meaningful changes in mean values from baseline for vital signs parameters within the treatment arms.

LRP/LUBT010/2016/008

Clinical Laboratory Evaluation

Tests for hematology, biochemistry and urine analysis were performed at Month 3, 6, 9, and 12 to assess the safety of patients. Abnormal values that were considered as clinically significant by the Investigator were reported as AEs.

Haematology

The proportion of patients who shifted from normal values at baseline to either low or high values at each endpoint was <10% patients in each treatment arm for all haematology parameters.

Blood Chemistry

The proportion of patients with shifts from normal values at baseline to either low or high values at each endpoint was <10% patients in each treatment arm for all biochemistry parameters, except for glucose.

Normal glucose values at baseline to high values:

- Month 3: 25 (8.4%) patients in the LUBT010 arm and 40 (13.3%) patients in the Lucentis arm,
- Month 6: 25 (8.4%) patients in the LUBT010 arm and 40 (13.3%) patients in the Lucentis arm
- Month 9: 40 (13.4%) patients in the LUBT010 arm and 34 (11.3%) patients in the Lucentis arm
- Month 12: 24 (8.0%) patients in the LUBT010 arm and 45 (15.0%) patients in the Lucentis arm.

Vital Signs, Physical Examination Findings, and Other Observations Related to Safety

There were no clinically meaningful changes in mean values from baseline for vital signs parameters within the treatment arms.

There were no clinically meaningful changes in the mean intra-ocular pressure (IOP) values from baseline within each treatment arm. A total of 7 (1.2%) patients reported TEAE of IOP increased, including 4 (1.3%) patients in the LUBT010 arm (1 patient with mild TEAE, 2 patients with moderate TEAE, and 1 patient with severe TEAE) and 3 (1.0%) patients in the Lucentis arm (all 3 patients reported mild TEAE).

No specific safety trend was observed in ECG findings during the study.

5.4.9. Post marketing experience

Not applicable.

5.4.10. Overall discussion and conclusions on clinical safety

5.4.10.1. Discussion

5.4.10.1.1. Overall assessment of available safety data

Comparability of safety of Vislyfa (further referred as Lupin ranibizumab, LUBT010) with the reference product EU-Lucentis was investigated in two clinical studies.

- **Study LRP/LUBT010/2022/001 (comparative PK study)**: randomised, open label, two-arm, parallel group study comparing the proposed ranibizumab biosimilar LUBT010 with EU-Lucentis in nAMD patients.
- **Study LRP/LUBT010/2016/008 (comparative efficacy and safety study)**: pivotal, randomised, double blind, two-arm, parallel-group study to demonstrate equivalent efficacy of LUBT010 to EU-Lucentis in patients with nAMD.

The applicant claimed the presentation of both the vial and the PFS. The clinical studies were conducted only with the vial dosage form. However, the comparability of vials and PFS was demonstrated accordingly at quality level. Thus, the applicant's claim is agreed by CHMP.

LUBT010 has been developed for the same adult indications as approved for licensed Lucentis in the EU: the treatment of adult patients with nAMD, DME, PDR, RVO, as well as CNV. Patients with nAMD were included in both clinical studies. The study population is deemed sufficiently sensitive to investigate biosimilarity as regards safety. The mechanism of action of ranibizumab is identical for all indications of Lucentis.

The safety database consisted of a total of 620 patients who received at least one dose of either LUBT010 or Lucentis in the two studies (study LRP/LUBT010/2022/001: 20 patients with nAMD and study LRP/LUBT010/2016/008: 600 patients with nAMD). The dose of LUBT010 administered in these two studies was 0.5 mg (0.05 mL of 10 mg/mL ranibizumab), which is consistent with the approved dose of Lucentis.

Due to the differences between the clinical studies with regard to the study design, treatment duration, pooling of safety data from the studies for the purpose of integrated analysis of the safety results could not be performed. However, the number of patients in the safety data set is deemed adequate for assessment of comparable safety of LUBT010 with EU-Lucentis in terms of biosimilarity.

Study LRP/LUBT010/2022/001

Safety assessments were performed after administration of a monthly IVT injection of 0.05 mg LUBT010 and EU-Lucentis in nAMD patients for 3 consecutive doses. The safety endpoints consisted of AEs, vital signs, physical examinations, 12-lead electrocardiogram tracing, laboratory parameters (haematology, biochemistry, and urinalysis) and ophthalmic examinations. Assessments were made at regular intervals, which is supported.

The study design is limited by the small sample size (total n of 20 patients) and the study duration was only a short-term evaluation, with the EOS occurring at Day 84. Therefore, the evidence for

equivalence of safety comes from study LRP/LUBT010/2016/008, while the safety results of study LRP/LUBT010/2022/001 are considered supportive of the primary results.

All 20 patients received all three ranibizumab doses and were included in the SAF.

A total of 6 (30.0%) patients reported TEAEs [3 (30%) patients each in the treatment arms]. The majority of TEAEs were of mild severity [2 (20%) patient each in the LUBT010 and Lucentis treatment arm]. One (10.0%) patient reported a moderate TEAE (PT cataract) in the LUBT010 treatment arm and one patient (10%) reported a severe TEAE (PT femur fracture) in the Lucentis treatment arm. The frequency and severity of the reported events are not considered clinically meaningful. None of them were reported as treatment-related, which is reassuring from a safety perspective.

The events of vertigo, blood glucose increased, back pain, haematoma, hypertension and fracture are generally not among the TEAEs known for ranibizumab (Lucentis SmPC). However, the TEAEs were isolated cases, of mild severity, and the patients recovered during the treatment phase. This is therefore not considered a cause of concern by CHMP. The event of femur fracture was classified as a severe AE. This SAE has been reported in the comparator treatment group and is probably due to chance. Hypersensitivity TEAEs or events of anaphylactic reactions were not reported in this study. There were neither study discontinuations nor deaths. Overall, the incidence of TEAEs was comparable between the LUBT010 and Lucentis treatment arms and reported AEs were not of concern.

Differences in the means (SD) for the actual values and change from baseline in lymphocytes, neutrophiles, platelet count as well as WBC count were noted but remained within normal ranges and no related adverse events occurred. Therefore, the haematological differences are not considered clinically relevant. Other results of the clinical laboratory measurements showed comparable values between the LUBT010 and the Lucentis treatment groups.

Ocular related safety parameters were examined including refraction examination, slit lamp examination, IOP measurement, indirect ophthalmoscopic examination, OCT and fluorescein angiography. The results of the ophthalmologic examinations did not reveal any relevant clinical differences.

Study LRP

LUBT010/2016/008

The design of the pivotal study LRP/LUBT010/2016/008 is considered adequate by CHMP to evaluate biosimilarity between LUBT010 and Lucentis in terms of safety/immunogenicity. The chosen posology of monthly IVT injection over a 12-month period is considered most appropriate from a safety perspective as a higher cumulative exposure is achieved in comparison to a treat-and-extend regimen. The study duration of 12 months is considered a relevant time period to assess comparative safety and immunogenicity.

The assessment of safety was overall sufficiently described in the protocol. The frequency of visits, observation period and outlined ophthalmic as well as other examinations are deemed adequate. The definition of AEs, the severity grading as well as the causality assessment appear appropriate.

The safety analysis set included all participants who received at least one dose of study intervention (LUBT010 n = 299, Lucentis n = 301). The mean (SD) duration of exposure was with 305.9 (77.27) and 311.4 (72.03) days overall comparable between treatment arms (LUBT010 and Lucentis, respectively). The majority of study participants (86.0% LUBT010, 89.4% Lucentis) had a duration of exposure ≥ 272 days and received >9 injections (87.0% LUBT010, 88.7% Lucentis), which is considered acceptable. There is a slightly longer duration by a mean of 6 days in the Lucentis arm,

likely linked to a higher study discontinuation in the LUBT010 arm (as further discussed in the clinical efficacy section). However, the numerical difference is considered not clinically relevant by CHMP.

No major imbalance in demographics and baseline characteristics was apparent, while the distribution of some ocular parameters remains unclear (clinical efficacy section). Concomitant medications and procedures were overall comparable between treatment arms.

TEAEs

156 (52.2%) and 163 (54.2%) patients reported **TEAEs** in the LUBT010 and Lucentis arm, respectively.

Ocular TEAEs

A comparable number of participants reported **ocular TEAEs in the study eye** (54 [18.1%] in the LUBT010 arm and 58 [19.3%] in the Lucentis arm). The reported ocular TEAEs are considered expectable and in line with (very) commonly reported ADR as per Lucentis SmPC. It was however noted that most ocular TEAEs occurred at lower-than-expected rates (as discussed below).

At the PT level, the most commonly reported ocular TEAEs were conjunctival haemorrhage (10 patients [3.3%] LUBT010 vs 14 patients [4.7%] Lucentis), cataract (2 patients [0.7%] LUBT010 vs 8 patients [2.7%] Lucentis), and dry eye (7 patients [2.3%] LUBT010 vs 1 patient [0.3%] Lucentis). A higher occurrence of dry eye in the LUBT010 treatment group compared to the Lucentis arm is noted. In addition, events of increased IOP were either reported as the PT "IOP increased" or "ocular hypertension" in different patients. Cumulatively, these events occurred more frequently in LUBT010-treated patients (7 [2.3%]) in comparison to Lucentis-treated patients (3 [1.0%]). The noted imbalance is due to a small numerical difference. However, 1 of the reported IOP events in the LUBT010 arm was severe. In addition, clinically singificant abnormalities in post-treatment IOP were reported in 2 LUBT010-treated patients and for none of Lucentis-treated patients. Slightly more patients experienced higher IOP post-dose elevations in the LUBT010 arm (5 patients who had IOP >40 mmHg in the LUBT010 arm vs 1 patient in the Lucentis arm; 4 of those with IOP >50 mmHg).

A transient spike in IOP within 60 minutes of Lucentis injection is a known effect of the treatment but also sustained IOP increases have been identified (Lucentis SmPC). It seems that there was no standardised approach regarding AE reporting related to IOP elevations. However, the mean and min/max changes from baseline pre-treatment were comparable between treatment arms, with no clear trend for a sustained increase in IOP over time, also not in patients reporting a TEAE of "IOP increased" or "ocular hypertension", which is reassuring for CHMP.

Regarding severity, most ocular TEAEs in the study eye were mild to moderate in severity. Severe TEAEs in the study eye occurred in 2 (0.7%) LUBT010-treated patients and in 6 (2.0%) Lucentis-treated patients. Regarding relationship to the study treatment, a slightly higher proportion of patients in the LUBT010 arm (7 [2.3%]) reported study-drug related TEAEs in comparison to the Lucentis arm (4 [1.3%]). Those encompassed predominantly single event occurrences of known (very) common ADRs reported for Lucentis, in addition to one report of endophthalmitis and non-infectious endophthalmitis in the Lucentis arm (uncommon ADR as per Lucentis SmPC) and one occurrence of macular hole in the LUBT010 arm, which is further discussed below. A comparable number of participants reported **ocular TEAEs in the non-study eye** (37 [12.4%] in the LUBT010 arm and 36 [12.0%] in the Lucentis arm.

Non-ocular TEAEs

A comparable number of participants experienced **non-ocular TEAEs** (118 [39.5%] in the LUBT010 arm and 116 [38.5%] in the Lucentis arm). The most commonly reported non-ocular ADRs according to the SmPC of Lucentis are nasopharyngitis, arthralgia and headache. Nasopharyngitis was among the

most frequently reported non-ocular TEAEs in the Lucentis arm (11 patients [3.7%]), with a higher occurrence in comparison to the LUBT010 arm (5 patients [1.7%]). The frequency of other very common Lucentis ADRs was largely comparable between treatment groups. Overall, these non-ocular TEAEs were reported at lower-than-expected rates in the present study. In addition, no major imbalance was apparent for other noted systemic events expected to be reported commonly according to the Lucentis SmPC between treatment arms.

Other non-ocular TEAE were overall comparable and if imbalances were noted, those are considered numerically small and thus, may also be a chance finding.

The majority of non-ocular TEAE were of mild to moderate intensity, with a comparable number of patients reporting severe events (12 [4.0%] LUBT010 vs 11 [3.7%] Lucentis), and none of these events were judged as related to the study drug. Regarding relationship, non-ocular TEAE were judged as related in 2 patients, both in the Lucentis arm. These events concerned one report of vertigo and one occurrence of cerebral ischaemia (with moderate severity). Noteworthy, vertigo is not a reported ADR as per SmPC of Lucentis and the cerebral ischaemia was apparently chronic and deteriorated.

In summary, the occurrence of ocular and non-ocular TEAEs is overall comparable between treatment groups, with no apparent systematic trends. The range of observed imbalances are deemed not clinically meaningful, and differences were numerically small. Thus, these observations are likely a chance finding rather than an indicator of differences in the ocular TEAE profile. It is noted that considering the study duration and the monthly IVT injections, the proportion of patients reporting TEAEs, especially ocular TEAEs, seems lower than expected and lower in comparison to other Phase 3 studies investigating ranibizumab biosimilars in the nAMD population that employed the same treatment schedule (Rimmyrah EMEA/H/C/006055/0000, Ximluci EMEA/H/C/005617/0000, Byooviz EMEA/H/C/005545/0000). Although outlined plans on the safety assessment procedures appear adequate, the lower occurrence of very commonly and commonly ADRs of Lucentis was noted. The applicant argued that investigators might consider certain events to be no longer reportable due to the clinical experience with IVT injections gathered over the years. The applicant's argumentation can in principle be followed although this does not entirely address the lower reporting frequency of (ocular) TEAEs in comparison to other recent biosimilar Phase III trials. Nevertheless, this would still result in an underreporting of events linked with a decreased sensitivity to detect differences between treatments, in case some exist. It is acknowledged that no meaningful qualitative and quantitative difference with regard to safety events was observable between treatment arms, although this issue remains as an uncertainty, without major impact, on the biosimilarity conclusion.

TESAEs

Ocular TESAEs

There were 7 **ocular TESAEs** reported in the **study eye**, with a slightly higher frequency in the Lucentis arm (5 patients [1.7%]) in comparison to the LUBT010 arm (2 patients [0.7%]). One TESAE of endophthalmitis was reported in both treatment arms, classified as not related in the LUBT010 arm and possibly related in the Lucentis arm.

One TESAE of macular hole was reported in 1 LUBT010-treated patient and evaluated as possible related. Additionally reported TESAE (retinal detachment, retinal haemorrhage, and cataract traumatic) were each reported in 1 patient in the Lucentis group and not judged as related.

Ocular TESAEs were reported with low frequency and are largely known ADRs for Lucentis as per SmPC. The causality assessment could not be followed in all instances. While it is agreed that many of the frequently reported ocular ADRs of Lucentis are linked to the administration procedure, such events are to be considered as drug related, as also outlined in the study protocol. However, this issue

will not be further pursued by CHMP as the incidence of ocular TEAE was overall comparable between treatment arms and no pattern was evident.

Non-ocular TESAEs

An overall comparable number of patients reported **non-ocular TESAEs** (22 [7.4%] LUBT010 vs 18 [6.0%] Lucentis), which were all not judged as related to the study drug.

According to Lucentis SmPC, there were potential events associated with IVT anti-VEGF treatment and its potential systemic effects that relate to cardiovascular and arterial thromboembolic events reported. In this pivotal study, cardiac disorders occurred in a comparable number of LUBT010- and Lucentis-treated patients (7 patients [2.3%] LUBT010 vs 5 [1.7%] Lucentis), while events of cerebrovascular accident, chest pain and ischaemic stroke occurred only in the LUBT010 group.

TEAEs that led to **death** were comparable between treatment arms (3 [1.0%] patients in the LUBT010 arm and 4 [1.3%] patients in the Lucentis arm) and none were judged as related to the study drug.

The reported TESAE and deaths generally raise no specific concern regarding the comparative safety between LUBT010 and Lucentis. Events were reported at low rates. The provided narratives could overall link the event occurrence to individual participant risk factors and medical history and additionally provided information regarding the timing of event occurrence of serious events related to cardiac disorders and nervous system disorders did not raise concerns.

It is considered likely that the study itself is not sufficiently sensitive to detect less common but potentially serious adverse events, such as ones linked to systemic anti-VEGF events. The systemic exposure with ranibizumab is expected to be low upon intraocular administration. However, comparative PK data is limited for LUBT010 and poses thus an uncertainty.

Study drug discontinuation due to **ocular** and **non-ocular** TEAE occurred in a small number of patients and no apparent pattern emerged. These events were mostly serious TEAEs and are discussed above. The frequency of study drug discontinuation is overall not concerning.

Overall no clinically meaningful difference in hematological, blood chemistry and urinalaysis changes between LUBT010-treated and Lucentis-treated patients is apparent. Comparable patterns were found in vital signs, slit lamp and indirect ophthalmoscopy findings.

5.4.10.2. Conclusions on clinical safety

Throughout the two clinical trials, the safety observations made by the CHMP were consistent with the established safety profile of the reference product Lucentis.

Overall, although the reporting frequency of (ocular) TEAEs for study LRP/LUBT010/2016/008 is noted by CHMP as an uncertainty, the submitted safety data support biosimilarity at clinical level.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 37: Summary of safety concerns in the proposed RMP

Important identified risks	• Infectious endophthalmitis • Intraocular inflammation • Retinal detachment and retinal tear • Intraocular pressure increase
Important potential risks	• None
Missing information	• None

6.1.2. Discussion on the proposed safety specification

The applicant proposed a summary of safety concerns as shown above.

The proposed summary of safety concerns is in line with the reference product's (Lucentis (ranibizumab)) latest approved RMP version 22.0 (date of final sign-off: 12 Oct 2022).

The important potential risk" Neurodevelopmental impairment (ROP)" is not included in the summary of safety concerns as it is only relevant for the ROP indication, which is accepted.

No additional safety concerns other than those reported for Lucentis were identified during the development of this biosimilar.

The summary of safety concerns is considered acceptable by the CHMP.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

The applicant proposed, in addition to routine pharmacovigilance activities, specific adverse reaction follow-up questionnaires to obtain collect further data and/or closely monitor the important identified risk of infectious endophthalmitis.

The applicant did not propose additional pharmacovigilance activities.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

The PRAC having reviewed the submitted data, is of the opinion that routine pharmacovigilance is adequate to identify and characterise the risks associated with the product. Furthermore, the PRAC considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the implemented risk minimisation measures (RMMs). The follow-up questionnaires proposed by the applicant are consistent with, and identical to, the follow-up checklist utilised by the originator. Thus, they are also endorsed by the PRAC.

6.2.2.2. Additional pharmacovigilance activities

The applicant did not propose any additional pharmacovigilance activities, which is acceptable for a biosimilar medicinal product.

6.3. Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned for Vislyfa.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 38: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Infectious endophthalmitis	**Routine risk minimisation measures:** **SmPC Sections:** Section 4.2 "Posology and method of administration" Section 4.3 "Contraindications", Section 4.4 "Special Warnings and Precautions" Section 4.8 "Undesirable effects" Section 6.6 "Special precautions for disposal and other handling" **PL Sections:** Section 4 "Possible side effects" **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for Endophthalmitis **Additional pharmacovigilance activities:** None
Intraocular Inflammation	**Routine risk minimisation measures:** **SmPC Sections:** Section 4.3 "Contraindications" Section 4.4 "Special Warnings and Precautions" **PL Sections:** Section 2 "What you need to know before you are given LUBT010" Section 4 "Possible side effects" **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Retinal Detachment and retinal tear	**Routine risk minimisation measures:** **SmPC Sections:** Section 4.4 "Special Warnings and Precautions" Section 4.8 "Undesirable effects" **PL Sections:** Section 2 "What you need to know before you are given LUBT010" Section 4 "Possible side effects" **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Intraocular pressure increase	**Routine risk minimisation measures:** **SmPC Sections:** Section 4.4 "Special Warnings and Precautions" Section 4.8 "Undesirable effects" Section 4.9 "Overdose" Section 5.3 "Preclinical safety data" **PL Sections:** Section 2 "What you need to know before you are given LUBT010" Section 4 "Possible side effects" **Pack size:** For vial: One vial (type I glass) containing 0.23 ml sterile solution. For PFS: one pre-filled syringe. **Legal status**: prescription only medicine **Additional risk minimisation measure:** Educational program for adult patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

In the proposed RMP, the safety concerns are aligned with the EU-RMP (V 22.0) of the reference medicinal product Lucentis. As no additional safety concerns (other than those reported for Lucentis) were identified during the development of this biosimilar, the routine RMM, as proposed by the applicant, are currently considered sufficient by PRAC.

6.4.2.2. Additional risk minimisation measures

Additional RMMs (aRMM) are in place for all the important identified risks: "Infectious Endophthalmitis, Intraocular Inflammation, Retinal detachment and Retinal tear and Intraocular pressure increase": specifically, a patient information booklet has been proposed.

These aRMMs, aligned with those implemented for the reference medicinal product Lucentis, are endorsed by PRAC.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.1 (dated 25 February 2026) is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Labelling

8.1.1. User consultation

A User testing of the Package Leaflet (PL) was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004. A justification for not performing a full user consultation on the PL with target patient groups was submitted by the applicant and found acceptable for the following reason:

- Consistent with the QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product (EMA/627621/2011), the applicant confirmed that, with the exception of differences based on scientific grounds, no deviations from the reference medicinal product's PL were introduced. Accordingly, no user testing consultation with target patient groups were conducted on the PL for Vislyfa (ranibizumab) 10 mg/mL solution for injection, as per Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vislyfa is included in the additional monitoring list since it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Biosimilarity assessment

9.1. Comparability exercise and indications claimed

Vislyfa (also referred to as LUBT010) was developed as a biosimilar to the reference medicinal product Lucentis. The administration route (IVT), posology, and indications are according to the reference product, as described in Lucentis SmPC.

The marketing authorisation is claimed, in adults, for:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein

occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

Quality

A comprehensive analytical similarity study was performed by the applicant for the purpose of demonstration of biosimilarity at the quality level between the proposed biosimilar and reference medicinal product (see Table 3: Analytical similarity assessment between Vislyfa and RefMP Lucentis).

Based on quality attributes criticality ranking approach, which is supported, evaluation plan has been adequately designed, and appropriate statistical methodology utilised for comparison of critical quantitative attributes (Mean ± 2/3SD; Mean ± X% (X being 1%, 5% or 10%)). Data clearly indicate similarity with EU RefMP.

Selection and number of the batches used for the biosimilarity exercise is considered acceptable.

Since FP manufacturing consists only of thawing of AS and filling into final container, use of mostly AS batches of the biosimilar for biosimilarity exercise is justified since it is demonstrated that no significant difference exists at the level of the quality between AS and FP quality that could influence conclusion on similarity.

Some of the RefMP and biosimilar batches were frozen before use in biosimilarity exercise or in comparative forced degradation study, to avoid shelf-life expiration before analysis. Although this approach is usually discouraged, it is acknowledged that low temperatures should not have significant impact on recombinant monoclonal antibody proteins quality. Results of the freeze thaw study using RefMP Lucentis and biosimilar product have been provided. In this study, samples were frozen at ≤-70 °C and thawed at room temperature (~ 25° C) for 3 freeze thaw cycles and analysed to check impact on different physicochemical and functional attributes. Choice of tests to analyse impact of freezing and thawing is endorsed and it can be concluded that unchanged quality of RefMP batches used in analytical biosimilarity exercise has been confirmed after freezing and thawing.

A comprehensive panel of analytical tests was used for the analytical biosimilarity exercise, which included orthogonal methods that measure different aspects of the same CQAs. The test panel is comprised of both, release and characterization assays. Panel covers primary, secondary, tertiary and higher order structure, product related impurities, potency and biological activity as well as product related attributes (protein content and sub-visible particles). All methods used for biosimilarity are either validated or qualified/fit for the intended purpose.

To further support biosimilarity claim, the applicant performed forced degradation study in which biosimilar and RefMP are compared under various stress conditions. Studies are in general designed in accordance with relevant EU guidelines and Scientific advice given has been followed.

Non-clinical data

As per the consolidated outcome of VEGF-A165 ELISA and SPR analyses with the different VEGF-A isoforms including VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A145, VEGF-A189, and VEGF-A206, similarity was established between Lucentis EU and Vislyfa with respect to biological activity, ligand binding and binding kinetics.

As per the joint results of HUVEC anti-proliferation assays and EFC assays for VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A145, and VEGF-A189, similarity was established between Lucentis EU and Vislyfa with respect to biological activity and potency.

The applicant also conducted a comparative pre-clinical toxicity study with LUBT010 in the rabbit. Of note: although this study has not demonstrated any meaningful differences between LUBT010 and Novartis Lucentis, the Lucentis used for this *in vivo* study was marketed in India. Therefore, it can't,

as such, be regarded in support of the biosimilarity approach between LUBT010 and EU-Lucentis.

Summary of clinical data

The clinical developmental program comprises of two clinical studies.

The pivotal Phase 3 efficacy and safety study **LRP/LUBT010/2016/008**, which was a randomised (1:1), double-blind, multiple dose (0.5 mg/kg per ITV injection every 4 weeks) parallel group study for a duration of up to 52 weeks comparing the efficacy, safety, immunogenicity between LUBT010 and EU-Lucentis in 600 subjects (299 LUBT010 and 301 Lucentis) with neovascular age-related macular degeneration.

PK was evaluated in the Phase 1 study **LRP/LUBT010/2022/001**, which was a randomised (1:1), open-label, parallel group study conducted in a total of 20 patients with nAMD in Country 2 (10 patients for LUBT010 and EU-Lucentis, respectively). Safety and immunogenicity were evaluated as secondary objectives, as well as an exploratory PD endpoint.

According to the applicant, the clinical development plan for Vislyfa (Lupin ranibizumab) was only aligned with the guidance documents relevant for the FDA, but Scientific advice was sought once from EMA [EMEA/H/SA/3346/1/2016/III], and most of the recommendations were implemented.

9.2. Results supporting biosimilarity

Quality

For all QAs tested in biosimilarity exercise, following is provided, where applicable: actual results for each batch analysed, min-max for biosimilar and RefMP, PLA graphs, spectra / chromatogram overlays, sensogram overlays, scattered plots, images.

Results presented demonstrate high degree of comparability to EU RefMP Lucentis for all quality attributes.

Regarding forced degradation comparability study, samples were evaluated for hydrophobic, size, charge and functional attributes, to evaluate the impact of stress condition on biological activity. Methods employed are stability indicating and endorsed. Under all the stress conditions for the attributes tested with analytical panel described above, the results demonstrate similar degradation profiles of Vislyfa and EU-approved Lucentis. Thus, based on the comparative analytical assessment and forced degradation studies it can be concluded that Vislyfa is similar to EU-approved Lucentis.

Non-clinical

VEGF-A165 ELISA and SPR analyses with the different VEGF-A isoforms including VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A145, VEGF-A189, and VEGF-A206, demonstrated similarity between Lucentis EU and Vislyfa with respect to biological activity, ligand binding and binding kinetics.

Clinical

Efficacy

Primary endpoint: the treatment difference for the mean change from baseline in BCVA at Month 12 was 0.03 ETDRS letters [95%CI: -1.82, 1.88] in the FAS population; the two-sided 95% CI was entirely within the pre-defined equivalence margin of ± 4 letters and also within a more clinically relevant ± 3 letter margin. The difference in the PPS was -0.39 letters and the 95% CI was also contained within the pre-defined margin (-2.25, 1.46). Supplementary analysis using a MMRM model supported the primary analysis in the FAS (LS mean difference [95% CI] LUBT010 vs Lucentis -0.28 [-2.21, 1.65]) and PPS (LS mean difference [95% CI] LUBT010 vs Lucentis -0.77 [-2.71, 1.17]).

Secondary endpoints: the mean BCVA change from baseline at earlier time points were evaluated as secondary endpoints and results were consistent with the 12-month analysis. The difference between the biosimilar and the RefMP at 3 months was 0.46 ETDRS letters [95%CI: -0.87, 1.79] in the FAS, which was supported by the results on the PPS (difference of -0.39 letters, with a 95% CI of -2.25, 1.46).

The proportion of patients who gained 15 letters or more in BCVA from baseline at Month 6 and Month 12 in the FAS was comparable between the two treatment arms LUBT010 and Lucentis.

Exploratory endpoint: the mean change in the NEI VFQ-25 composite score is comparable between the LUBT010 and Lucentis treatment arm (LUBT010: 4.40, Lucentis; 3.78 at month 3; LUBT010: 9.59, Lucentis: 9.25 at month 12, in the FAS).

Safety

The biosimilarity of LUBT010 and EU-Lucentis was demonstrated in two clinical trials, both conducted in adult patients with nAMD. The safety database consisted of a total of 620 patients who received at least one dose of either LUBT010 or Lucentis (Study LRP/LUBT010/2022/001: 20 patients with nAMD; Study LRP/LUBT010/2016/008: 600 patients with nAMD).

The safety findings observed were overall in line with Lucentis SmPC. No new or unexpected safety issues have been identified.

An overall comparable number of participants reported **ocular TEAEs** in the study eye (54 [18.1%] in the LUBT010 arm and 58 [19.3%] in the Lucentis arm). The most commonly reported ocular TEAEs were conjunctival haemorrhage (10 patients [3.3%] LUBT010 vs 14 patients [4.7%] Lucentis), cataract (2 patients [0.7%] LUBT010 vs 8 patients [2.7%] Lucentis), and dry eye (7 patients [2.3%] LUBT010 vs 1 patient [0.3%] Lucentis). The reported ocular TEAEs are considered expectable and in line with (very) commonly reported ADR reported for Lucentis. Only a few severe ocular TEAEs occurred in the study eye (2 [0.7%] LUBT010-treated patients and 6 [2.0%] Lucentis-treated patients). The frequency of **ocular TESAE** was low (2 patients [0.7%] LUBT010, 5 patients [1.7%] Lucentis) and the reported events were consistent with the known safety profile of Lucentis.

A similar proportion of patients reported **non-ocular TEAEs** (118 [39.5%] in the LUBT010 arm and 116 [38.5%] in the Lucentis arm). The majority of non-ocular TEAE were of mild to moderate intensity, with a comparable number of patients having severe events (12 [4.0%] LUBT010 vs 11 [3.7%] Lucentis). **Non-ocular TESAE** were reported at low rate.

Supporting evidence stems from study LRP/LUBT010/2022/001, which showed a comparable safety profile. The incidence of TEAEs was similar between the treatment groups and most TEAEs were of mild or moderate severity.

Uncertainties and limitations about biosimilarity

Quality

None.

Non-clinical

For the repeat dose toxicity study India-sourced Lucentis was used as a comparator to LUBT010. Thus, the study results are not to be considered for the overall biosimilarity assessment. However, there is no impact on the overall assessment as repeat dose toxicity studies are not required for the MAA of biosimilars for the EU market.

Clinical

Efficacy

No anatomical endpoints were evaluated in the pivotal study. Therapeutic biosimilarity demonstration is therefore based solely on BCVA changes and are not supported by anatomical endpoints (e.g. CFT), which are a more objective measure as compared to BCVA.

Baseline characteristics regarding CNV lesion type and lesion size were not documented.

During a routine EMA GCP inspection at two study sites and the sponsor, one site-specific critical finding and several major findings at the site- and sponsor-level were identified. The critical finding concerned manipulation of essential metadata of IOP measurements and a general lack of understanding for essential GCP principles, which was considered a site-specific issue and an isolated case. One major finding particularly concerned the fitness of the blinding solution to detect tampering based on an IMP kit presented during to the inspection and it remained unclear whether all kits employed in the clinical trial were fit for purpose. Overall, the pivotal study LRP/LUBT010/2016/008 was considered not fully ICH GCP compliant.

Safety

The proportion of patients reporting TEAEs, especially ocular TEAEs, seems lower than expected.

Immunogenicity

The presented results indicated that the incidence of baseline ADA- and treatment-emergent ADA-positive patients was higher than reported for historical studies.

Pharmacokinetics

The number of patients enrolled in the PKS is small (n=20). Hence, the comparative PK data is limited for the biosimilar exercise.

The systemic concentrations of ranibizumab measured close to C_{max} after the 1st and 3rd IVT injections indicated a slight underexposure of LUBT010.

The mean maximum concentrations of Vislyfa and Lucentis were above the concentration range of ranibizumab that was necessary to inhibit the biological activity of vascular endothelial growth factor by 50% (Lucentis SmPC).

9.3. Discussion on biosimilarity

Quality

The applicant’s approach for demonstrating biosimilarity is mostly aligned with the relevant EMA guidelines and thus considered acceptable. The selection of batches and assignment of criticality of quality attributes (QAs) for the comparative assessment is presented and is considered largely acceptable.

A large panel method has been used to characterise and compare the most relevant physicochemical and biological quality attributes of the ranibizumab molecule and is considered acceptable. Summaries of the methods used in the comparative analytical assessment studies are provided in the dossier and data was presented to show that these methods were suitably qualified for the purpose of comparability.

The results presented herewith demonstrate that Vislyfa displays high degree of comparability to EU Lucentis for all quality attributes including protein content, identity, primary, secondary, and tertiary structure, purity, levels of product-related variants such as size, charge, and hydrophobic variants, and levels of other product-related variants including oxidized and deamidated variants. Potency by cell-based

assays and ELISA as well as binding kinetics to various VEGF-A isoforms are similar for Lucentis EU and Vislyfa. Overall, Vislyfa is similar to EU-approved Lucentis.

Non-clinical

Ranibizumab was aimed for intraocular use, targeted against human VEGF-A. VEGF-A is key factor mediating angiogenesis, binding of VEGF-A to its receptors lead to endothelial cell proliferation, vascular leakage which contribute to progression of AMD. Among multiple isoforms generated from alternate splicing of VEGF-A gene, VEGF165, VEGF121 and VEGF110 are three predominant biologically active soluble isoforms in *in vivo*. Ranibizumab binds to all these three isoforms with high affinity. Thus, Ranibizumab neutralizes VEGF-A isoforms and precludes binding of VEGF-A to its receptor henceforth inhibiting activation of downstream signalling cascade which leads to advancement of AMD.

Based on this special mechanism of action of Ranibizumab, *in vitro* pharmacology testing was performed. The *in vitro* testing for LUBT010, which included cell-based assays and ligand binding covering the potency and primary target ligand, indicated, that the *in vitro* binding and functional activity of LUBT010 is similar to the RefMP Lucentis authorized in the EU. Although some differences were observed for two LUBT010 batches (in the study "Potency by VEGF-A121 EFC Assay using HEK293-KDR/KDR cells"), this is likely due to inherent method variations and is specific to this assay. However, the same LUBT010 batches complied with the two-sided QR when analysed with an orthogonal functional assay for VEGF-A121 binding (binding kinetics by SPR).

Although a further *in vivo* comparability study has not demonstrated any meaningful differences between LUBT010 and Novartis Lucentis, the Lucentis used for this *in vivo* study was marketed in India and is as such not in support of the biosimilarity approach between LUBT010 and EU-Lucentis.

Clinical

The pivotal comparative efficacy and safety study in neovascular AMD patients evaluating the proposed biosimilar LUBT010 and EU-Lucentis is overall adequately designed. Biosimilarity was demonstrated as the primary efficacy endpoint *Mean change of BCVA from baseline at Month 12* in the FAS population was met. Results were supported by sensitivity analyses and outcomes obtained in the PPS. Although the 12-month evaluation is not the most sensitive outcome, analyses investigating the treatment difference at 3 months were consistent with 12-month data, which was also observable in additionally requested sensitivity analyses. Notwithstanding, therapeutic biosimilarity is not supported by anatomical measures, which would be more objective than BCVA. This is considered an important shortcoming of the clinical program. Nevertheless, the totality of data is considered sufficient to overcome this uncertainty, as further outlined below.

Safety and immunogenicity were investigated in a sufficiently large number of patients for a biosimilarity exercise, and the study duration of 12-month is appropriate. The occurrence of ocular and non-ocular TEAEs was overall comparable between treatment groups. The range of observed imbalances are deemed not clinically meaningful, and differences were numerically small. However, the proportion of patients reporting TEAEs, especially ocular TEAEs, seems lower than expected. Although current data indicate a comparable safety profile, also with no specific trend regarding serious events related to cardiac and nervous system disorders, the sensitivity to detect potential differences between treatments may be decreased due to underreporting.

The presented immunogenicity results indicate comparable ADA and (low) NAb incidence between LUBT010- and Lucentis-treated patients, which is in principle supportive for biosimilarity. It was noted that the ADA-positivity rate at baseline as well as upon treatment appears generally higher than expected based on historical originator data. An investigation conducted by the applicant confirmed the validity of the immunogenicity dataset. Given the absence of any difference in the cumulative incidence of antibodies between the two treatment arms, and the low likelihood of identifying a definitive cause, no further

investigation was being pursued. Despite the unclear background of this observation, the increased incidence of ADA positivity was balanced between the study arms; thus, equivalent immunogenicity can be assumed.

Systemic concentrations measured close to C_{max} after the first and third IVT injections indicated a slight underexposure of LUBT010 compared to Lucentis. However, due to the small study size, the data are too limited to make an entire conclusion about the clinical relevance of this difference. Of relevance is the finding that the maximum serum concentrations observed (2 patients in each study arm) are higher than expected and are above the concentration range of ranibizumab (11-27 ng/mL) that was necessary to inhibit the biological activity of VEGF-A by 50% (Lucentis SmPC). However, no patient experienced safety concerns associated with systemic VEGF inhibition. These results suggest that the higher C_{max} values do not translate into an increased incidence of AEs that could potentially be related to systemic VEGF inhibition.

From a clinical perspective, efficacy is considered comparable, as the primary analysis met the predefined equivalence margins, and the secondary and exploratory endpoints further substantiated this conclusion. The safety profile also appears broadly similar. Nevertheless, several deficiencies at the clinical level were identified, including significant GCP findings and the absence of an anatomical endpoint in the pivotal Phase 3 study. Although the critical GCP finding was considered a site-specific, isolated case and efficacy, safety and immunogenicity results are comparable when excluding data from the non-compliant site (which enrolled overall only 7 patients), it is notable that GCP non-compliance and data manipulation related to IOP measurements were seemingly not detected earlier, despite regular monitoring visits. Notwithstanding, considering the conclusion and recommendation from the integrated GCP inspection report, the data obtained from the pivotal Phase 3 study are acceptable although several uncertainties at the clinical level remain, which cannot be addressed retrospectively. Despite these limitations, the totality of the biosimilarity exercise is considered, which also entails comparability conducted at quality and functional levels. Importantly, biosimilarity at the quality level is considered robust.

9.4. Extrapolation of safety and efficacy

The applicant claims the presentation of the vial and the PFS. While the clinical studies were only conducted with the vial presentation, the provided comparability exercise between the vial and the PFS presentation demonstrated comparability at the quality level. Thus, extrapolation for the PFS is possible.

The mechanism of action of LUBT010 is identical to the reference product Lucentis. The monoclonal antibody ranibizumab targets and binds to VEGF-A, preventing the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation. Thus, the subsequent growth of new blood vessels is prevented. The mode of action has been adequately described by the applicant. In addition, the applicant described that the mechanism of action is identical across all indications.

It is agreed that there is comparability across the authorised Lucentis adult indications (AMD, DME, PDR, RVO, and CNV) concerning the target, mode of action, safety and immunogenicity. Thus, based on the same mechanism of action, demonstrated similarity in quality and extended functional characterization, as well as clinical evidence, extrapolation to all adult indications of Lucentis is supported.

9.5. Additional considerations

Not applicable.

9.6. Conclusions on biosimilarity and benefit risk balance

In conclusion, based on the review and totality of the submitted data, Vislyfa is considered biosimilar to Lucentis. Therefore, a benefit/risk balance comparable to the reference product can be concluded.