9 November 2023
EMA/CHMP/536323/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rimmyrah

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/006055/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AKT	Protein kinase B
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
AP-ROP	Aggressive posterior retinopathy of prematurity disease
ATE	Arterial thromboembolic events
BCVA	Best corrected visual acuity
BMI	Body mass index
CD	Circular dichroism
CDC	Complement dependent cytotoxicity
CE-SDS	Sodium dodecyl sulfate capillary gel electrophoresis
CEX-HPLC	Cation exchange chromatography
CFT	Central foveal thickness
CI	Confidence interval
CNV	Choroidal neovascularisation
CPT	Centre point thickness
CRT	Central retinal thickness
CSR	Clinical Study Report
CTD	Common technical document
CZE	Capillary zone electrophoresis
DCO	Data Cut-Off
DME	Diabetic macular oedema
DR	Diabetic retinopathy
DRSS	DR severity score
EEA	European Economic Area
ERK	Extracellular signal-regulated kinase
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
Fab	Fragment antigen binding
FAS	Full analysis set
FCP	Foveal centre point
FCS	Foveal central subfield
FTIR	Fourier-transform infrared spectroscopy
HMW	High molecular weight
HUVEC	Human umbilical vein endothelial cell
IEF	Isoelectric focusing
Ig	Immunoglobulin
IgG	Immunoglobulin G

IOP	Intraocular pressure
ISI	Integrated Summary of Immunogenicity
IVT	Intravitreal
L	Liter
LC-MS	Liquid chromatography–mass spectrometry
LloQ	Lower limit of quantification
LMW	Low molecular weight
LOQ	Limit of quantitation
LS	Least squares
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measurements
n	Number
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
ns	Not statistically significantly different
OCT	Optical coherence tomography
PD	Pharmacodynamics
PDR	Proliferative diabetic retinopathy
PDT	Photodynamic therapy
PK	Pharmacokinetics
PlGF	Placental growth factor
PM	Pathologic myopia
PPS	Per-protocol set
PRP	Panretinal photocoagulation
PT	Preferred term
ROP	Retinopathy of prematurity
RP-HPLC	Reverse phase high-performance liquid chromatography
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety analysis set
SD-OCT	Spectral-domain optical coherence tomography
SE-HPLC	Size exclusion-high performance liquid chromatography
SOC	System organ class
SV-AUC	Sedimentation velocity analytical ultracentrifugation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	Unites States
UV	Ultraviolet
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
wAMD	wet (neovascular) age-related macular degeneration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant QILU PHARMA SPAIN S.L. submitted on 7 October 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Rimmyrah, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2021.

The applicant applied for the following indication:

Rimmyrah 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)

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products, The application submitted is composed of administrative information, complete quality data, appropriate nonclinical and clinical data for a similar biological medicinal product.

The chosen reference product is a medicinal product which is or has been authorised in accordance with Union provisions and to which biosimilarity has been demonstrated by appropriate studies:

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

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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 because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
15 November 2018	EMEA/H/SA/3961/1/2018/III	*Juha Kolehmainen, Andrea Laslop*
22 April 2021	EMA/SA/0000053924	*<Name>, <Name>*

The Scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

Quality

- Testing plans for the Master Cell Bank and the Working Cell Bank and End of Production Cells
- Specifications for drug substance and drug product
- Source of the reference medicinal product

Non-Clinical

- Need for in-vivo studies

Clinical

- Primary and secondary endpoints
- Equivalence margin and sample size
- Sample size calculation
- Multi-regionality of the trial
- Extrapolation to other indications
- Pharmacokinetic sampling
- Submission of data package for a MAA.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Frantisek Drafi

The application was received by the EMA on	7 October 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 January 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2023

The applicant submitted the responses to the CHMP consolidated List of Questions on	13 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 October 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
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 Rimmyrah on	9 November 2023

2. Scientific discussion

2.1. About the product

Rimmyrah (QL1205) was developed as a proposed similar biological medicinal product to Lucentis (INN: ranibizumab; ATC code S01LA04), having ranibizumab as active substance. Lucentis was initially registered via the Centralised Procedure in the European Union (EU) in 2007.

Ranibizumab, the active substance of Rimmyrah, is a recombinant humanized monoclonal antibody fragment composed of a light chain linked by a disulfide bond at its C-terminus to the N-terminal segment of the heavy chain that binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF-A165. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to pathophysiology of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to choroidal neovascularization (CNV), and retinopathy of prematurity (ROP). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR-1 and VEGFR-2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

With the initial MAA, the applicant applied for all approved indications, including the paediatric ROP indication (treatment of retinopathy of prematurity with zone I, zone II or AP-ROP disease).

However, with his response to the D120 LoQ, the applicant has decided to withdraw the claim for the Lucentis-approved indication treatment of retinopathy of prematurity (ROP) in pre-term infants.

The claimed therapeutic indications for Rimmyrah hence is 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)

The proposed administration route (intravitreal injection) and posology proposed for Rimmyrah are identical to those for the reference medicinal product, Lucentis.

2.2. Quality aspects

2.2.1. Introduction

The finished product (also designated QL1205) is presented as sterile solution for intravitreal administration containing 10 mg/mL ranibizumab as active substance.

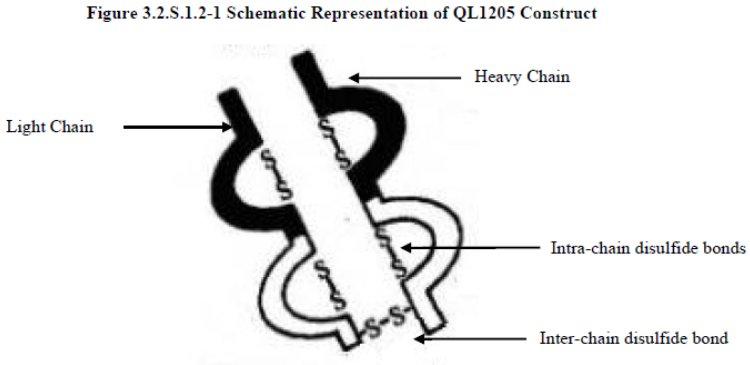
Other ingredients are: α,α-trehalose dihydrate, polysorbate 20, histidine and histidine hydrochloride monohydrate buffer.

The product is available as two presentations: a vial packaged in a carton, or a combination of a vial and a filter needle co-packaged in a carton.

2.2.2. Active Substance

2.2.2.1. General Information

Figure 1. Schematic molecular structure



The active substance of QL1205 is the Fab moiety of a recombinant humanised IgG1 kappa isotype monoclonal antibody. It binds to and inhibits the biological activity of human vascular endothelial growth factor A (VEGF-A). The active substance is expressed in *Escherichia coli* (*E. coli*) cells. The molecule is a heterodimer consisting of a kappa light chain and an N-terminal half of IgG1 heavy chain. QL1205 contains 10 cysteine residues forming 4 intra-chain and 1 inter-chain disulfide bonds. Potency is tested by an anti-proliferation bioassay (HUVEC) and a binding assay (ELISA) for routine release and stability testing.

The applicant has provided sufficient general information regarding QL1205.

2.2.2.2. Manufacture, process controls and characterisation

2.2.2.2.1. Manufacture

QL1205 active substance is manufactured and tested at the following site:

- Qilu Pharmaceutical Co., Ltd., 8888 Lvyou Road, High Tech Zone, Jinan, Shandong, 250104, China (DUNS: 544532200)

Only a QP declaration under MIA 6317 belonging to the batch release site KYMOS, S.L., (Ronda De Can Fatjó 7 B, Parc Tecnològic Del Vallès, Cerdanyola Del Vallès, Barcelona, 08290, Spain) was available in the initial submission. Remote audits took place in February 2022. Inspections were performed by AEMPS from May 29, 2023 to June 2, 2023, to the active substance and Finished product manufacturers, i.e. Qilu Pharmaceutical Co., Ltd., 8888 Lvyou Road, High Tech Zone, Jinan, Shandong, 250104, China. GMP compliance was confirmed to be satisfactory.

Description of manufacturing process and process controls

QL1205 active substance is produced by *E. coli*. The manufacturing process consists of fermentation process and purification process.

Reprocessing is not allowed except in case of filter integrity test failure of active substance.

Process flow charts for the upstream fermentation process and the downstream purification process are provided. Process parameters and in-process controls with acceptance criteria are indicated.

Overall, the information provided is deemed sufficient.

Control of materials

A tabulated overview of compendial and non-compendial raw materials used in the production process is provided. In-house specifications for non-compendial raw materials are in place. There are no raw materials of human origin used during the manufacture of QL1205. In the upstream process, two biologically sourced raw materials are used. In the downstream process, only one biologically sourced raw material is used. The applicant confirms that the biologically sourced raw materials meet the requirements outlined in the European guideline "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01-Rev 3)".

The origin, source, history of cells and generation of the cell substrate has been sufficiently described, in line with principles and recommendations given in ICH Q5B. The construction of the expression vector is sufficiently described and includes a detailed component map with list of functional components. The recombinant vector was sequenced and confirmed to exactly match the expected QL1205 DNA sequence.

A two-tiered cell bank system consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB) was established. The cell banks were characterized in line with ICH Q5D guideline. Results provided so far demonstrate that the cell banks are stable over storage.

PPQ batches were manufactured according to the determined production process, and the end-of-production cells (EOPC) was tested. The EOPC was tested for purity, identity and genetic stability. Test results met the requirements. A brief description of the characterization test methods has been provided in the dossier. Test methods used for screening of cell banks have been suitably qualified.

A protocol for establishing future cell banks has been provided. The newly prepared WCB will be tested, characterised, and qualified prior to use in line with the requirements of the original WCB. The information provided is deemed sufficient.

Control of critical steps and intermediates

Each Critical Process Parameter (CPP), Key Process Parameter (KPP) and non-Key Process Parameter (non-KPP) is classified for the proposed commercial process based on their impact on Critical Quality Attributes (CQAs). A CPP is a process parameter whose variability has impact on CQAs, and therefore must be monitored and maintained to ensure acceptable product quality. A KPP is a process parameter that need to be monitored to ensure process performance consistency and robustness, but is not critical for CQAs. A Non-KPP is a process parameter which is easily controlled and has no impact in quality or performance within wide ranges. The classification of the parameters is further discussed in module S.2.6 of the dossier.

For the QL1205 active substance manufacturing process CPPs have been identified in the purification process.Most of the parameters have been classified as KPPs. The manufacturing process is controlled by in-process controls.

Throughout the manufacturing, process intermediates may be held for a short period of time. The hold times were validated during the PPQ runs.

Process validation

Performance of the active substance manufacturing process was verified at commercial site and scale using consecutive process validation batches.

The data from process validation was evaluated for the set-point and the NOR/AOR obtained from process characterization studies. The validation results, which were all within their specified acceptance criteria, demonstrate that the process performs consistently and delivers active substance complying with the release specifications under commercial operating conditions.

The cleaning process for QL1205 active substance manufacturing was validated. Test results showed that residues after cleaning procedures met the acceptance criteria.

Overall, the process has been demonstrated to be capable of removing process related impurities, product-related impurities and contaminants.

For filter validation reference is made to module 3.2.P.3.5.

Hold time studies were conducted for media, buffers and process intermediates. Extractables/leachables studies were conducted for product contact materials. No toxicological assessment and leachable studies were conducted. Original reports for the extractables studies are provided in module 3.2.R.5 of the dossier. For the QL1205 active substance no formal shipping validation has been performed. This is deemed acceptable since the thawed active substance is transported to the finished product facility located in the adjacent building. The approach is supported by accelerated stability studies.

Manufacturing process development

During the manufacturing process development of the QL1205 active substance, different manufacturing processes were developed.

Comparability:

To support process changes, comparability studies have been conducted in accordance with recommendations provided in the ICH Q5E guideline. Comparability has been sufficiently demonstrated.

Active substance process characterisation studies:

Process characterisation started with a risk assessment of the process parameters at each process stage based on the critical quality attributes (CQAs). Quality attribute of the product were classified based on the efficacy or activity, PK/PD, immunogenicity, and safety aspects using a risk ranking approach. Overall, the assignment of CQAs is deemed adequate.

Subsequently, potential critical process parameters (pCPP) and potentially key process parameters (pKPP) in the active substance production process that could affect CQAs were determined using a risk assessment.

Selected process parameters were evaluated in process characterisation studies. Scale-down models were established and process characterisation experiments were conducted using a combination of univariate and multivariate studies. Acceptable operating ranges (AOR) and normal operating ranges (NOR) were determined.

Potential critical/important process parameters (pCPP/pKPP) for each process stage of active substance production are scored according to risk level.

Classification of CPPs, KPPs and IPCs is considered appropriate.

2.2.2.2.2. Characterisation

For characterisation, PPQ batches were analysed.

A range of state-of-the-art orthogonal methods were used including physicochemical and biological testing in accordance with ICH Q6B guideline. The analytical methods used in characterisation studies are qualified to be suitable for their intended use.

As determined by LC-MS, the molecular masses of the analysed samples correspond to the expected theoretical value. LC-MS/MS peptide mapping revealed 100 % identity of the amino acid sequence compared to the Lucentis amino acid sequence. UV peptide mapping chromatograms are highly similar to each other in PPQ batches. QL1205 disulfide linkages are consistent with expected linkages. The amounts of free thiols in QL1205 are below the limit of quantitation of the assay.

In summary, the characterisation of QL1205 is considered adequate. It is noted that in section S.3.1 mainly the similarity of the results for the PPQ batches was discussed. A discussion on the implications for structure and characteristics of the molecule is sometimes missing (e.g. near and far UV CD).

Impurities

Measurement of product-related impurities, process-related impurities as well as adventitious agents were performed during release testing of QL1205 active substance PPQ batches.

Additional potential process-related impurities were tested in the PPQ batches with qualified methods. The results demonstrate that the residual levels of these impurities are well below the corresponding threshold assessed by toxicology and impurity safety factor, and are not considered as safety risk.

Process capabilities to clear impurities is also discussed in section S.2.5 of the dossier.

2.2.2.3. Specification

The release specification for QL1205 active substance include tests for appearance, identity, purity and impurities, process-related impurities, quantity, potency, microbial safety, and general attributes. For the compendial methods reference has been made to the respective Ph. Eur monographs. For non compendial methods refrence to SOP is given.

Overall, the set of release parameters tested complies with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008.

Descriptions for the analytical methods are sufficiently detailed. Development of a product specific method is ongoing and the applicant committed that a variation will be submitted by 2nd Quarter 2024 (REC).

During development several analytical methods were changed or improved. Method bridging studies have been conducted for the other tests.

Validation of analytical procedures

Non-compendial analytical methods have been sufficiently validated and are suitable for their intended use. Original validation reports are provided. The validation experiments were performed with QL1205 reference standard or finished product samples. The characteristics mentioned in the current ICH Q2 guideline have been considered for method validation.

Batch analyses

QL1205 active substance has been manufactured using different processes. The batch release data shows consistent and comparable quality of QL1205 active substance manufactured across all batches of process development. All the active substance batches comply with the pre-established specifications valid at the time of testing.

Justification of specification

Specification limits were established mainly based on batch release data. After tightening of several specification limits), specification limits are now considered adequate.

Reference standards

During development of QL1205 several reference standards were sourced. The first generation reference standard was obtained from a Process 1 batch and used for toxicology research. The second generation reference standard was also obtained from a Process 1 batch and used for phase I and III clinical studies. The first and second generation reference standards are superseded. The current primary reference standard was obtained using QL1205 finished product from a clinical batch, and will be used to support the commercial manufacturing.

A working reference standard (WRS) has recently been established to be used for the releasing of future commercial batch and stability testing. The working reference standards has been qualified against the primary reference standard. Qualification was performed as for the current primary reference standard. A protocol for the preparation of future working reference standards has been provided.

2.2.2.3.1. Container closure system

Specifications, technical drawings and a representative vendor certificate for the container closure system have been provided. Compatibility has been demonstrated by stability studies. Product-contact materials comply with compendial requirements for the packaging of medicinal products. The bottle is free from bovine spongiform encephalopathy (BSE) and other transmissible spongiform encephalopathies (TSE).

Extractables and leachables studies have been conducted. Based on the test results of extractable studies, leachable studies with quantitative testing method and full scan method were performed using commercial-scale active substance. The test results indicated that the elements in the active substances did not exceed the 50% limit and the organics did not exceed AET. Leachables studies should continue until the end of active substance shelf life to confirm the compatibility between the active substance and its container closure system. Overall, information on the container closure system is considered sufficient.

2.2.2.4. Stability

The design of the registration stability studies is in line with ICH Q5C guideline. Overall, the parameters tested resemble the active substance release specifications. Process-related impurities, primary sequence and microbial attributes are not part of the stability program, which is acceptable.

A confirmatory photostability study was conducted, and it has been demonstrated that the active substance quality is not affected during the production and storage.

A commitment to complete the currently ongoing stability studies is provided. In addition, at least one commercial batch of QL1205 active substance will be placed in the long-term stability program at -20°C ± 5°C per year during production years.

Overall, the provided stability data support a shelf-life at the recommended storage condition for QL1205 active substance.

2.2.3. Finished Medicinal Product

2 . 2 . 3 . 1 . Description of the product and Pharmaceutical Development

2.2.3.1.1. Description and Composition of the Finished Product

The QL1205 finished product is a sterile solution for intravitreal administration. The finished product is supplied in two presentations: a vial packaged in a carton, or a combination of a vial and a filter needle co-packaged in a carton. The filter needle, being a medical device, has been assessed by a Notified Body and has a CE mark.

The finished product is formulated as 10 mg/mL ranibizumab in α,α-trehalose dihydrate, polysorbate 20, histidine and histidine hydrochloride monohydrate buffer.

The finished product is filled in a Type I glass vial with a chlorobutyl rubber stopper and an aluminium-plastic combination cap. Each vial contains 2.3 mg of ranibizumab in a 0.23 mL labelled volume.

The composition of the finished product is adequately described.

QL1205 active substance is formulated at a target protein concentration in α,α-trehalose dihydrate, polysorbate 20 and histidine and histidine hydrochloride monohydrate buffer.

Finished product

The dosage form, and strength of QL1205 were determined to be the same as those of reference product Lucentis.

There are no overages in the production of QL1205 finished product.

Manufacturing Process Development

As for active substance, different finished product manufacturing processes were developed.

During process development, no changes were introduced to the dosage form, formulation, excipients and primary packaging materials. Overall, it is noted that there were no major process changes between the processes used to manufacture the clinical batches.

- Comparability:

To support process changes comparability studies have been conducted in accordance with recommendations provided in the ICH Q5E guideline. Comparability at release was determined. Samples from different processes can be considered comparable. Comparative stability studies (long-term, accelerated and stressed condition) were also conducted. The stability trends are consistent and comparable. Extended characterisation testing was also performed. All testing results demonstrate that the finished product batches are comparable.

- Process characterisation:

Process characterisation was initiated with the establishment of the quality target product profile (QTPP) for the finished product and identification of the critical quality attributes (CQAs) for the finished product. A risk based categorization of all process control parameters with potential impact on quality attributes was performed using failure mode effect analysis (FMEA) that categorizes the process parameters into critical process parameters (CPP), key process parameters (KPP) and non-KPP. Subsequently, process characterisation experiments were conducted on selected process parameters.

The normal operating ranges (NOR) of CPP and KPP for the production process of finished product were determined.

Overall, process characterisation studies are described in detail and are deemed relevant.

The quality specifications of the container closure systems are provided. The glass vial and chlorobutyl rubber stopper used meet the requirements of Ph. Eur. 3.2.1 and Ph. Eur. 3.2.9 respectively. There is no risk of TSE/BSE.

Container closure integrity was tested by both vacuum decay method and microbial ingress method. The results confirm that no leakage was detected.

Extractables studies have been conducted. No elemental impurities above the thresholds mentioned in ICH Q3D guideline have been observed. The test results of non-volatile organics, semi-volatile organics, volatile organics and special organics did not exceed analytical evaluation threshold (AET).

As demonstrated by the stability data presented in module 3.2.P.8 the finished product is compatible with the container closure system.

Microbiological attributes

QL1205 finished product is a single dose vial and no preservatives are included in the formulation. Sterility is assured by control of raw materials, the aseptic filling process, release specifications and integrity of the container closure system.

Compatibility

The route of administration of the finished product is intravitreal injection. Multiple studies were conducted during clinical development to assess the use and compatibility of QL1205 finished product with the syringe and needles including dosing accuracy, deliverable volume, adsorption, extractable and leachable study and in-use stability.

Overall, pharmaceutical development of QL1205 is adequately described.

2.2.3.2. Manufacture of the product and process controls

Manufacturers

QL1205 finished product is manufactured and tested at the following site:

- Qilu Pharmaceutical Co., Ltd., 8888 Lvyou Road, High Tech Zone, Jinan, Shandong, 250104, China (DUNS: 544532200)

Importation and batch release testing is performed at KYMOS, S.L., (Ronda De Can Fatjó 7 B, Parc Tecnològic Del Vallès, Cerdanyola Del Vallès, Barcelona, 08290, Spain). Respective Manufacturing and Importation Authorisation and GMP compliance certificate have been provided for this site.

Only a QP declaration under MIA 6317 belonging to the batch release site KYMOS, S.L., was available in the initial submission. Remote audits took place in February 2022. Inspections were also performed by AEMPS from May 29, 2023 to June 2, 2023, to the active substance and finished product manufacturers, i.e. Qilu Pharmaceutical Co., Ltd., 8888 Lvyou Road, High Tech Zone, Jinan, Shandong, 250104, China. GMP compliance was confirmed to be satisfactory.

Description of manufacturing process and process controls

QL1205 finished product is manufactured according to a standard manufacturing process (fill-and-finish) for monoclonal antibody-based products.

Hold times are supported by hold time studies in section P.3.5. and P.3.2.

Re-processing is not allowed during the finished product manufacturing processes.

Controls of critical steps and intermediates

The finished product manufacturing process is controlled by process parameters and in-process controls. Critical process parameters and in process controls have been identified and seem appropriate for control of the process. Intermediates are adequately controlled. Applied hold times have been validated.

For IPC methods which are not used for active substance or finished product release, applicant concludes that verification / validation is not required. This is supported, since these methods are equipment dependant and qualification of the equipment is under GMP remit.

Process validation and/or evaluation

Prior to the process validation studies, risk assessment and process characterisation studies were conducted in order to define process parameters and their effective ranges. Based on these studies, all process parameters which may impact the product quality and/or process performance were examined and classified as critical process parameters (CPP), key process parameters (KPP), non-critical process parameters (Non-CPP) and non-key process parameters (Non-KPP).

Process Performance Qualification:

For process validation, consecutive finished product PPQ batches were employed. The calculated theoretical batch sizes is considered validated.

All process parameters as well as performance parameters monitored during the process validation studies were maintained within their specific ranges for all process validation batches. Based on the data provided, it can be concluded that the QL1205 finished product process is robust and consistently delivers QL1205 finished product of the anticipated quality. Ranges have been studied and defined during process characterization studies and are considered justified. None of the ranges was challenged during process validation.

Continued process verification is foreseen for CQAs and other process parameters. Validation of sterilisation processes has been adequately described.

To confirm whether the transportation conditions from the manufacturing site to the EU have any effects on finished product quality, shipping validation studies were conducted. It is confirmed that container closure integrity and finished product quality is not affected by transportation.

Product specification, analytical procedures, batch analysis

2.2.3.2.1. Control of Finished Product

The release specification for QL1205 finished product include tests for appearance identity purity and impurities visible and sub-visible particles, quantity potency microbial safety and general attributes For the compendial methods reference has been made to the respective compendial monographs. Limits for sub-visible particles are set according to USP <789>. Since there is no corresponding requirement for ophthalmic products in the Ph. Eur., this approach is accepted.

In accordance with ICH Q3D Guideline for elemental impurities, a comprehensive risk assessment for elemental impurities potentially present in QL1205 was performed in terms of manufacturing equipment, drug substance, water, excipients and container closure system.

Overall, the set of release parameters tested complies with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008.

Analytical procedures

For the in-house analytical methods the descriptions are sufficiently detailed and acceptable. For methods used for both active substance and finished product reference has been made to module 3.2.S.4.2. During development several analytical methods were changed or improved. The methods are considered equivalent. This conclusion can be agreed.

Validation of analytical procedures

All analytical methods used for release testing of QL1205 finished product have been appropriately validated based on the principles provided in ICH Q2 guideline. Validation of analytical procedures common to active substance and finished product are presented in module 3.2.S.4.3 of the dossier.

Established compendial procedures, are performed in accordance with the specified compendial method and have not been validated. Some of them have been verified, while for other methods, that are depended on instruments, verification is not performed. Since those are compendial methods (Ph. Eur. or USP), this is considered acceptable.

The presented validations for analytical methods are acceptable and demonstrate the suitability of the analytical procedures for their intended use. Confirmation regarding transfer of the methods – validation of methods at EU batch release site is also provided.

Batch analyses

QL1205 finished product has been manufactured using different processes. The batch release data shows consistent and comparable quality of QL1205 finished product manufactured across all batches of process development. All batches comply with the pre-established specifications valid at the time of testing.

Characterisation of impurities

No new impurities have been introduced during the QL1205 finished product manufacturing process and reference is made to module 3.2.S.3.2 of the dossier.

Furthermore, elemental impurities and extractables/leachables derived from manufacturing process components have been addressed in section 3.2.P.3.5 of the dossier. No risks were identified. The levels of each elemental impurity in the product were tested (3 batches). All test results for elemental impurities analysis are well below the LOQ, which are consistently and significantly below the control threshold (30% of the established PDE). Conclusively, no additional controls are required.

In accordance to ICH M7(R1), EMA/369136/2020, EMA/409815/2020, a risk assessment for nitrosamine impurities was performed in the production and storage of QL1205 active substance and finished product. No risk was identified.

Justification of specification

Specification limits were established mainly based on batch release data and based on stability data Following tightening of several specification limits upon request and taking into account the ranges obtained for reference medicinal product, specification limits are now considered adequate.

Reference Standards or Materials

The same reference standard as for the active substance is used. No other product-specific reference standards are used in the testing of the finished product. Reference is made to section 3.2.S.5.

Container Closure System

The finished product container closures system consists of a Type I glass vial, a chlorobutyl rubber stopper and a aluminium-plastic combination cap. The primary packaging materials comply with the European Pharmacopoeia. Manufacturer compliance statements are provided.

There are two presentations for QL1205 finished product: vial only pack and vial and filter needle pack. For the later presentation, the co-packaged filter needle (18G x 1½, 1.2 mm x 40 mm, 5 µm) is certified by a Notified Body and has a CE-mark.

Secondary packaging for both presentations consists of a carton designed to protect the vial from light and potential physical damage during handling, shipping, and storage.

Extractables studies have been conducted. No elemental impurities above the thresholds mentioned in ICH Q3D guideline have been observed. The test results of non-volatile organics, semi-volatile organics, volatile organics and special organics did not exceed analytical evaluation threshold (AET). Subsequently, a leachable study was conducted on QL1205. PPQ batches were used to carry out leachables study by validated methods. The test results indicated that the elements did not exceed the 50% limit and the organics did not exceed AET, so toxicological evaluation was not required. Detailed information is provided in section P.2.4. Leachables studies should continue until the end of finished product shelf life to confirm the compatibility between the finished product and its container closure system.

2.2.3.3. Stability of the product

The proposed long term storage condition for QL1205 finished product is 5°C ± 3°C. A shelf-life of 36 months is proposed, based on long-term primary stability data (real-time, recommended storage conditions)

The stability specification for QL1205 finished product comprises a reduced set of parameters. For all of the parameters, the acceptance criteria of the stability specifications are identical to those of the release specifications.

The design of the registration stability studies is in line with ICH Q5C guideline. Overall, the parameters tested resemble the active substance release specifications – except for identity testing which is omitted. All stability batches were manufactured at Qilu Pharmaceutical Co., Ltd., (8888 Lvyou Road, High Tech Zone, Jinan, Shandong, 250104, China) and stored in representative container closure systems.

Additionally, stability studies have been conducted light stress, freeze/thaw stress and vibration stress.

A photostability study in line with ICH Q1B guideline has been conducted using the PPQ batches. The study showed that QL1205 finished product is light sensitive. Upon photo exposure a significant degradation in the samples were observed; No significant changes were observed in other quality attributes. A commitment to complete the currently ongoing stability studies is provided. In addition, at least one commercial batch of QL1205 active substance will be placed in the long-term stability program at 5°C ± 3°C per year during production years.

Stability protocol has been provided and includes stability indicating parameters, which is endorsed.

Overall, the presented data for QL1205 finished product support the intended shelf-life of 36 months according to the principles outlined in ICH Q5C.

2.2.3.4. Biosimilarity

A comprehensive biosimilarity evaluation for demonstration of a comparable quality profile of QL1205 and its medicinal reference product Lucentis has been conducted. An adequate number of lots of EU-Lucentis has been analyzed using various analytical methods to establish the quality ranges to determine the similarity between QL1205 and the reference medicinal product.

Table 1. Analytical test panel used for biosimilarity exercise

The analytical test panel for the similarity exercise was as follows:

Molecular parameter	**Attribute**	**Methods**	**Key findings, conclusions**
Primary structure	Intact mass analysis (non-reduced)	LC-MS	Similar
	Intact mass analysis (reduced)	LC-MS	Similar
	Amino acid sequence	reduced peptide mapping LC-MS/MS	Identical
	UV peptide mapping	RP-UPLC	Similar
Disulfide linkages	Disulfide linkages	Non-reduced peptide mapping LC-MS/MS	Similar
	Free thiol	Fluorometry	Similar
Higher order structure	Secondary structure	Circular Dichroism (far UV)	Similar
	Tertiary structure	Circular Dichroism (near UV)	Similar
	Secondary structure	FTIR	Similar
	Tertiary Structure	Fluorescence Spectroscopy	Similar
	Thermal stability	DSC	Similar
	Higher order structure	Hydrogen-Deuterium Exchange (HDX) Analysis	Similar
Post-translational Modification	Deamidation	LC-MS/MS	Similar
	Succinimide	LC-MS/MS	Similar
	Oxidation	LC-MS/MS	Similar
	N-Terminal Glutamate Cyclization	LC-MS/MS	Similar
	Methylation	LC-MS/MS	Similar

	Truncation	LC-MS/MS	Similar
	Norleucine (Nle)	LC-MS/MS	Similar
	Norvaline (Nva)	LC-MS/MS	Similar
General attributes	Protein Concentration	UV (absorbance at A278)	The protein concentration results of two batches are out of the similarity range. However, the totality of evidence indicates that QL1205 is similar to EU-Lucentis.
	Extinction Coefficient	Kjeldahl method	Similar
Identity	Isoelectric point	icIEF	Similar
Purity and impurities	Main peak and LMWS	nrCE-SDS	Similar
	LC+HC and LMWS	rCE-SDS	Similar (slightly higher purity for QL1205)
	Monomer and HMWS	SE-HPLC	Similar
	Monomer and HMWS	AUC	Similar
	Acidic peaks, main peak, and basic peaks	IE-HPLC	Similar
	Hydrophobic variants	HI-HPLC	Similar
	Residual Host Cell DNA	qPCR	Similar
	Residual HCP	HCP ELISA	Similar
	Endotoxin	Gel clot method	Similar
	Particulate matter	MFI	Similar
	Particle size distribution and polydispersity	DLS	Similar
Potency	Biological activity	Cell based Bioassay (VEGF-A165)	Similar
	Biological activity	Cell based Bioassay (VEGF-A121)	Similar
	Biological activity	Cell based Bioassay (VEGF-A110)	Similar

	Biological activity	Cell based Bioassay (VEGF-A189)	Similar
	Biological activity	Binding Assay (VEGF-A165)	Similar
	Cell migration	Cell migration (VEGF-A165)	Similar
	VEGF-A165 binding	Antigen binding affinity VEGF-A165	Similar
	VEGF-A121 binding	Antigen binding affinity VEGF-A121	Similar
	VEGF-A110 binding	Antigen binding affinity VEGF-A110	Similar
	VEGF-A189 binding	Antigen binding affinity VEGF-A189	Similar

A large panel of standard and state-of-the-art methods has been used to characterize and compare the most relevant physicochemical and biological quality attributes of the ranibizumab molecule, demonstrating biosimilarity. Analytical methods have been qualified or validated. Results of method qualification/validation are provided. Methods can be regarded suitable for their intended use.

Quality attribute risk ranking

Structure, activity, product composition and contaminants of the product were directly assigned as critical quality attributes (CQAs). For the criticality of other quality attributes a risk ranking approach was followed, which considers the possible impact, and uncertainty of the impact on each attribute. Quality attributes were ranked according to (a) their risk to potentially impact efficacy, PK/PD, immunogenicity, safety, and (b) the degree of uncertainty surrounding a certain quality attribute. Overall, quality attribute risk ranking is considered adequate.

Statistical analysis plan

Assignment of statistical analysis and corresponding acceptance criteria for the physicochemical and biological quality attributes was based on the criticality risk ranking of the quality attributes.

Biosimilarity criteria as set are in general acceptable. However, for certain QAs, the approach itself is not endorsed. Nevertheless, since the majority of the results of biosimilarity exercise complies with more narrow criteria (except for protein content, see later in the report), this is accepted.

The description of the statistical approach for setting the acceptance criteria is deemed acceptable. Although the ±3 SD range for attributes with high and medium criticality is considered wide and not meaningful, no impact on the overall conclusion on biosimilarity is expected. The overall conclusion on biosimilarity is based on the measured values and results provided. Therefore, no question will be posed on the statistical approach.

Reference standards

In the similarity study, two different reference standard lots were used. In the results tables it is indicated which of the two standards was used. A bridging comparative study was conducted on the

quality and structure of the two lots of reference standards. The results show that the reference standards are comparable. The use of two different reference standards does not raise any concerns.

Analytical Similarity

The results of the structural and physicochemical properties, biological activity and binding assay comparative study between QL1205 and EU-Lucentis showed that QL1205 are within the similarity range determined by tested EU-Lucentis lots.

Furthermore, a comparative stability study using both QL1205 and the reference medicinal product Lucentis (EU-sourced) has been conducted. Thermal stress, light stress, oxidative stress and pH stress showed an impact on QL1205 finished product stability. A decrease in purity parameters is observed. Overall, the results were similar for QL1205 finished product and the reference medicinal product Lucentis.

Comparative stability

Comparative forced degradation studies were conducted between QL1205 and EU-Lucentis to show the similarity in the degradation kinetics. Stability studies were conducted at accelerated temperature condition, photostability, high temperature, pH stress and oxidative stress. Trending graphs are provided for protein concentration, IE-HPLC main peak, SE-HPLC main peak, nrCE-SDS main peak, rCE-SDS LC+HC, and potency by cell-based bioassay. Similar stability patterns are observed for EU-Lucentis and QL1205. It is however noticed that neither EU Lucentis nor QL1205 samples show significant degradation pattern in stressed conditions, as it would be expected. Only values for main peak detected by IE-HPLC at 45°C ± 2°C, pH 3.4 downtrend slightly. This is not observed for monomer by HE-HPLC at the same conditions. Although this is quite unusual, no concern exists since in validation of analytical methods, more extreme conditions were used on validation samples resulting in observable degradation of the product. In addition suitability of analytical methods to detect degraded product has been demonstrated.

Overall, the conclusion that QL1205 has a comparable quality profile with EU-sourced Lucentis is agreed and biosimilarity demonstrated.

2.2.3.5. Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been demonstrated. The active active substance is produced in a serum-free culture medium. The MCB is free from TSE-risk substances.

Virus safety

The fermentation process of QL1205 is in a serum-free medium. This minimises a possible contamination for adventitious viruses. The cells used for production of QL1205 however are of bacterial origin (*E.coli*), therefore no virus safety testing on cell banks and un-processed bulk has been performed.

In summary, the safety of QL1205 (ranibizumab biosimilar) has been sufficiently demonstrated.

2.2.3.6. Medical devices

There are two presentations for QL1205 finished product: vial only pack and vial and filter needle pack. For the later presentation, the co-packaged filter needle (18G x 1½, 1.2 mm x 40 mm, 5 µm) is certified by a Notified Body and has a CE-mark according to the MDD. A compliance statement from the device manufacturer is provided and an MDR Certificate will be available.

Information for the filter needle is provided in line with the "Guideline on quality documentation for medicinal products when used with a medical device" (EMA/CHMP/QWP/BWP/259165/2019) for co-packaged device. Filter needle for withdrawal of vial content is the same as for the reference product. This makes it suitable for use with QL1205 biosimilar product. Usability studies can be waived for the same reason. Supporting documentation and specifications of the filter needle are provided in section P.7. Information on the selection of the filter needle and compatibility with QL1205 finished product can be found in section P.2. The SmPC, labelling and package leaflet do not include details of the device manufacturer, CE mark, device symbols, etc.

The information regarding the medical device is considered sufficient.

2.2.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

QL1205 has been developed as a biosimilar to the reference medicinal product EU-Lucentis. It is a Fab moiety of a recombinant humanised IgG1 kappa isotype monoclonal antibody which selectively binds to vascular endothelial growth factor (VEGF-A) - and thereby inhibits the binding of VEGF to its receptors (VEGFR-1 and VEGFR-2) on the surface of endothelial cells.

Module 3 of the dossier is of adequate quality.

The finished product is supplied in two presentations: a vial packaged in a carton, or a combination of a vial and a filter needle co-packaged in a carton. The co-packaged filter needle is certified by a Notified Body and has a CE-mark according to the Medical Device Directive (MDD).

The manufacturing process of the active substance and finished product, together with the control strategy; characterisation; pharmaceutical development; specifications; and stability are sufficiently addressed.

QL1205 active substance and finished product are manufactured and tested at two manufacturing sites. GMP status of these sites was confirmed during the procedure.

Process changes during development have been sufficiently addressed with no issues identified. Representativeness of small scale models used in the development was confirmed.

Process validation has been performed for consecutive active substance and finished product batches. Consistent in-process and release data confirm that the manufacturing process is consistent and robust.

Active substance and finished product specifications ensure consistent quality of the QL1205 active substance and finished product. Specifications and acceptance criteria include those commonly encountered for a monoclonal antibody. Methods description and validation of the methods were updated with additional data/information/revisions provided during the procedure. Kymos S.L. Spain is importation, testing and batch release site in EU, it has been demonstrated that the transfer of all non-compendial analytical methods to the respective QC testing sites has been completed.

For reference standard clarifications are requested.

A comprehensive and robust biosimilarity exercise demonstrates similarity of the proposed biosimilar candidate with its reference medicinal product EU-Lucentis – except for protein concentration which was out of the determined similarity range for two QL1205 batches. Overall, protein concentration is considered as a critical quality attribute for ensuring accurate clinical dosing and the difference was adequately justified. All other physicochemical and biological attributes have been demonstrated to be similar.

From the quality perspective, QL1205 is approvable as a biosimilar to the reference medicinal product EU-Lucentis.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Herwenda is approvable from the quality point of view.

2.2.6. 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:

The applicant should present up to 36 months real time data obtained for the active substance leachables study once available. Moreover, the applicant should also immediately communicate to the agency any issues observed in the course of the study.

Results from ongoing leachables studies until the end of finished product shelf life should be provided as they become available. The applicant should also immediately communicate to the agency any issues observed in the course of the study.

The applicant currently develops a process-specific HCP assay. As committed by the applicant, the variation to introduce the new HCP assay should be provided.

2.3. Non-clinical aspects

2.3.1. Introduction

The legal basis for this application refers to Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for biosimilar medicinal products.

Rimmyrah is developed as a biosimilar of Lucentis, and is a recombinant humanized anti-human VEGF-A (human vascular endothelial growth factor A) monoclonal antibody Fab fragment, which has a small molecular weight and advantage in drug permeability.

Rimmyrah is an injectable liquid intended for intravitreal injection administration at a concentration of 10 mg/mL, which is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), and visual impairment due to choroidal neovascularisation (CNV).

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

The primary pharmacodynamics of QL1205 was investigated using four in vitro binding studies and two cell-based assays. Binding to VEGF-A121, -A110, and -A189 proteins were detected by SPR and binding to VEGF-A165 protein was detected by SPR and ELISA. Furthermore, proliferation of HUVEC cells (expressing VEGF receptors) was inhibited with comparable efficacy by Rimmyrah or EU-Lucentis. A cell migration assay (VEGF-A165) in HUVEC cells demonstrated comparable inhibition efficacy of Rimmyrah and EU-Lucentis. The data were also included into the analytical similarity study and support the biosimilarity of Rimmyrah to Lucentis (please refer also to the discussion of module 3). Further SPR analyses showed that Rimmyrah had high affinity to human VEGF-A165, -A121, -A112, and canine

VEGF-A164, and had low affinity to rat and no affinity to mouse VEGF-A164. These data support the use of the animal models in the in vivo studies. No binding was detected by SPR towards human VEGF-B, VEGF-C, VEGF-D and PIGF, consistent with the reference medicinal product. The in vivo effect of Rimmyrah was evaluated in a rhVEGF-induced vascular permeability test in Guinea Pigs. In general the results showed comparable inhibition for Rimmyrah in comparison to Lucentis. Slight differences especially at the low dose group might be attributed to the high variability of the test system. The origin of the Lucentis reference medicinal product (EU or non-EU) is not stated. However, as the data are only considered supportive no concern is raised on this issue.

In a Laser-induced Choroidal Neovascularization (CNV) Model in Rhesus Monkeys Rimmyrah and Lucentis showed comparable inhibitory effects on leakage areas and retinal thickness. Again, the origin of the Lucentis reference medicinal product (EU or non-EU) is not stated. However, as the data are only considered supportive no concern was raised on this issue.

2.3.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted. A literature review of secondary pharmacology (from FDA (BLA application number 125156)) was provided. This is considered adequate.

2.3.2.3. Safety pharmacology programme

In general safety pharmacology studies are not required for similar biological medicinal products. Nevertheless, examination of safety pharmacology parameters of the cardiovascular system (blood pressure, electrocardiography) and additionally general conditions (behaviour) were included into the repeat-dose toxicity study in Rhesus monkeys. As expected from data from the Lucentis MAA no effect on the cardiovascular system was detected in either the Rimmyrah or the Lucentis treatment groups. Again, the origin of the Lucentis reference medicinal product (EU or non-EU) is not stated. However, as the data are only considered supportive no concern is raised on this issue.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted, which is adequate for this biosimilar development.

2.3.3. Pharmacokinetics

ELISA methods were used for the detection of Rimmyrah and Lucentis in the serum and eye tissues or ADA detection in the serum. The assays were sufficiently validated and the limits of detection are considered acceptable for both materials (Rimmyrah and marketed Lucentis).

The comparability of PK parameters between Rimmyrah and Lucentis was investigated in two in vivo studies in rhesus monkeys (one single dose PK study and one repeated dose toxicity study). The applicant provided supportive literature summaries on preclinical PK of Lucentis, which support the designs of the studies (route of administration and dose levels). The non-GLP data from the first PK study showed comparable distribution of Lucentis and Rimmyrah in the tested tissues (lens, iris, choroid, retina, vitreous, aqueous humor and serum) after IVT administration. The two Rimmyrah dosages used showed dose-proportional exposure with low accumulation. The frequency of ADA development was low for both Rimmyrah and Lucentis with no effect on exposure.

In general drug concentrations in vitreous and aqueous humor were greatly higher than those in other tissues, which is in line with the literature data. In summary, the PK of Rimmyrah and Lucentis is considered comparable from a non-clinical perspective based on the two Rhesus monkey study data.

No studies on distribution, metabolism, excretion and pharmacokinetic drug interactions were conducted, which is acceptable.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

A single dose toxicity study was performed in rhesus monkeys, with a high and low dose of QL1205. Due to the limited number of animals (one animal per dose level) the explanatory power of the study is considered low. However, as the study would not have been expected for this biosimilar program no concern is raised. After the IVT administration in stage one a second administration via intravenous injection was performed in stage 2 to guarantee sufficient serum exposure to investigate systemic toxicity. No toxicology relevant findings were reported.

2.3.4.2. Repeat dose toxicity

To compare the toxicology of Rimmyrah with its reference medicinal product Lucentis a 6-Week IVT toxicity study with a 4-week recovery was performed in rhesus monkeys. A high and low dose level of Rimmyrah, a low dose level Lucentis and a vehicle group were included. The study length and recovery phase are considered adequate. It is noted that this study would not have been requested for this biosimilarity program as it is not considered necessary based on the analytical and in vitro comparability results and is not expected to provide relevant results in terms of biosimilarity conclusion. The results of the tested parameters do not show any test article-related toxicology. The only findings (one in the Rimmyrah low dose and two in the vehicle group) can be attributed to injection induced lens/vitreous opacity. ADAs were detected in both Rimmyrah and Lucentis treated animals. From the antibody production probability, time, and titers, there was no significant difference in immunogenicity between the two antibodies. Hence, in summary there were no differences in the toxicology between Rimmyrah and Lucentis as expected.

2.3.4.3. Genotoxicity

No genotoxicity study has been performed in line with ICH S6 (R1) and EMA/CHMP/BMWP/403543/2010.

2.3.4.4. Carcinogenicity

No carcinogenicity study has been performed in line with ICH S6 (R1) and EMA/CHMP/BMWP/403543/2010.

2.3.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity have not been performed in line with ICH S6 (R1) and EMA/CHMP/BMWP/403543/2010. Furthermore, such studies have not been performed for EU-Lucentis and a respective statement is included into the SmPC.

2.3.4.6. Toxicokinetic data

The toxicokinetics were in general comparable between Rimmyrah and Lucentis. No major sex differences or accumulation were reported. The exposure was comparable between bot products and there was a dose-dependent increase seen for the high dose Rimmyrah dose group.

2.3.4.7. Local Tolerance

A dedicated eye irritation test was performed in Japanese white rabbits by instillation into the conjunctival sac. The relevancy of the study results is in general considered limited as the administration differs significantly. Nonetheless, a separate local tolerance test would not have been requested for the biosimilarity program. Furthermore, the data from the repeated dose toxicity study do not suggest issues considering local tolerance. Therefore, no concern is raised. The provided data show no irritant effects as would have been expected.

2.3.4.8. Other toxicity studies

An antigenicity assessment was included into the repeated dose toxicity study in rhesus monkeys. The incidence of ADA development was low and comparable between both materials (Lucentis and QL1205). The ADAs were also shown to poses varying neutralizing activity. In general, the relevancy of ADAs in animal models is considered limited in comparison to the human situation. In conclusion the data show comparable results and no concern is raised.

Furthermore, an immunotoxicity assessment was included into the repeated dose toxicity study in rhesus monkeys. As expected given the low systemic exposure after IVT injection no immunotoxicity effects were reported.

A dedicated hemolysis effect study was performed using rabbit red blood cells. No effect on hemolyses or agglutination has been reported, which is in line with the literature from studies using human or cynomolgus monkey whole blood samples.

2.3.5. Ecotoxicity/environmental risk assessment

In the case of biosimilars, an environmental risk assessment is not needed; nevertheless, the applicant provided a justification for its absence which was considered acceptable.

2.3.6. Discussion on non-clinical aspects

The legal basis for this application refers to Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for biosimilar medicinal products.

Rymmyrah was developed as a biosimilar to the European Union (EU) Reference Medicinal Product Lucentis. Rimmyrah is a recombinant humanized anti-human VEGF-A (human vascular endothelial growth factor A) monoclonal antibody Fab fragment, which has a small molecular weight and advantage in drug permeability.

Rimmyrah is an injectable liquid intended for intravitreal injection administration at a concentration of 10 mg/mL, which is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), and visual impairment due to choroidal neovascularisation (CNV).

The applicant provided data from several non-clinical studies (pharmacodynamic, pharmacokinetic and toxicology) to support the biosimilarity of Rimmyrah to the reference medicinal product Lucentis. Regarding the applicable Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) non-clinical in vivo studies are not considered necessary if the analytical biosimilarity studies do not raise concerns which need to be further investigated in the non-clinic. Given the good comparability between Rimmyrah and the reference medicinal product non-clinical in vivo studies would not be warranted and are

discouraged. To meet global requirements the applicant performed several in vivo studies and provided the results in order to provide all available data sets for review. In general, these data are considered supportive in terms of this MAA, especially as non-EU-Lucentis has been used in the in vivo studies.

The PD studies Rimmyrah to Lucentis included several non-clinical in vitro studies have been conducted, investigating the binding to VEGF isoforms, related molecules and the biological effect of ranibizumab. The data show good comparability for both materials. Three EU-marketed Lucentis batches were compared to four Rimmyrah batches. Furthermore, three China and US-licensed reference medicinal product batches were included as supportive information.

Even though not expected for this biosimilar development, as laid down in the EU guidances on biosimilars and given the good comparability on the physico-chemical in vitro analytical level, non-clinical in vivo studies have been performed and the data provided. The studies included pharmacodynamic studies in rhesus monkeys and guinea pigs. Furthermore, effects on the cardiovascular system (safety pharmacology) were included into the repeated dose toxicology study in rhesus monkeys. As expected, no significant differences were detected between both materials supporting the good comparability on the physico-chemical in vitro analytical level. Of note, the origin of the Lucentis reference medicinal product (EU or non-EU) is not stated for the in vivo studies. However, as the data are only considered supportive, no concern is raised on this issue.

The comparability of PK parameters between Rimmyrah and Lucentis was investigated in two in vivo studies in rhesus monkeys (one single dose PK study and one repeated dose toxicity study). The applicant provided supportive literature summaries on preclinical PK of Lucentis, which support the designs of the studies (route of administration and dose levels). The non-GLP data from the first PK study showed comparable distribution of Lucentis and Rimmyrah in the tested tissues (lens, iris, choroid, retina, vitreous, aqueous humor and serum) after IVT administration. The two Rimmyrah dosages used showed dose-proportional exposure with low accumulation. The frequency of ADA development was low for both Rimmyrah and Lucentis with no effect on exposure.

In general drug concentrations in vitreous and aqueous humor were greatly higher than those in the other tissues, which is in line with the literature data. In summary, the PK of Rimmyrah and Lucentis is considered comparable from a non-clinical perspective based on the two Rhesus monkey study data.

No studies on distribution, metabolism, excretion and pharmacokinetic drug interactions were conducted, which is acceptable.

The applicant performed several in vitro and in vivo toxicological studies, none of which is considered pivotal and of high relevance for the current MAA. The studies are summarised and assessed above. Overall, no unexpected findings were observed.

In the case of biosimilars, an environmental risk assessment is not needed, the applicant’s justification is acceptable.

In conclusion, there are no concerns regarding the biosimilarity of Rimmyrah to marketed EU-Lucentis from a non-clinical point of view.

2.3.7. Conclusion on the non-clinical aspects

Overall, the nonclinical package is considered acceptable and no unexpected results were observed. Given the non-pivotal nature of the studies and the absence of unexpected results or findings, no other concerns were raised for clarity. From the nonclinical point of view, no major differences were observed between Rimmyrah and the EU-sourced comparator.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

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

The applicant has 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.

- **Tabular overview of clinical studies**

Table 2. Overview of the Clinical Development Plan

Table 2.5-1 Overview of the Clinical Development Plan

Study	Study Objectives	Design	Study Population	Primary Endpoints
QL1205-001 Phase 1 (China) wAMD subjects	Primary objective: To conduct preliminary evaluation on the clinical safety after intravitreal injection of QL1205 or Lucentis in patients with wAMD. Secondary objectives: To conduct preliminary evaluation on the clinical efficacy and PK characteristics after intravitreal injection of QL1205 or Lucentis in patients with wAMD.	Randomised, double-blind, parallel, positive (Lucentis)-controlled study; Total duration: 12 weeks; Intravitreal injection 0.5 mg (0.05 mL) once every 4 weeks for 3 consecutive doses, either QL1205 or Lucentis	48 Chinese wAMD subjects (23 for QL1205, 25 for Lucentis)	Safety: To conduct preliminary evaluation on the clinical safety after intravitreal injection of IMP.
QL1205-002 Phase 3 (UK, China/India) subjects	Primary objective: To demonstrate QL1205 was equivalent to Lucentis in subjects with wAMD. • To evaluate the efficacy of QL1205 versus Lucentis in subjects with wAMD based on CFT, area of CNV, and leakage from CNV lesion. • To evaluate the systemic exposure of QL1205 versus Lucentis in subjects participating in PK evaluation. • To evaluate the safety or QL1205 versus Lucentis.	Randomised, double-masked, parallel-group, multiregional, multicentre study; Total duration: 52 weeks; Intravitreal injection 0.5 mg (0.05 mL) once every 4 weeks for 13 consecutive doses, either QL1205 or Lucentis	616 wAMD subjects (308 for QL1205, 308 for Lucentis)	Efficacy: BCVA letters at Week 8 compared to Baseline using the ETDRS protocol.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Rimmyrah has been developed as a similar biological medicinal product ("biosimilar") to Lucentis®. The administration route (intravitreal injection), posology, and indications are according to the reference medicinal product, Lucentis®.

Two clinical studies were performed for Rimmyrah from which PK and immunogenicity data were obtained: a clinical Phase 3 study in patients with wAMD (QL1205-002) and a supportive clinical Phase 1 study in patients with wAMD (QL1205-001) conducted in China (as requested by the Chinese CDE).

The pivotal Phase 3 study, Study QL1205-002, was a randomised, double-masked, parallel group, multicenter study to compare the efficacy, safety, pharmacokinetics and immunogenicity between Rimmyrah and Lucentis in subjects with wAMD. PK analysis was performed in a subset of 73 subjects, including 33 subjects for Rimmyrah and 40 subjects for Lucentis.

The supportive Phase 1 study, Study QL1205-001, was a randomised, double-blinded, parallel-group, active-controlled Phase 1 study to compare the safety, PK, and PD of Rimmyrah and Lucentis (China) in patients with neovascular (wet) age-related macular degeneration (wAMD). Exploratory analysis on efficacy and PK was performed. PK analysis was performed in a subset of 48 subjects, including 23 subjects for Rimmyrah and 25 subjects for Lucentis.

A standalone comparative clinical Phase 1 PK study was not conducted to support this application. In addition, no further clinical studies on the PK of Rimmyrah in the paediatric population have been conducted.

Bioanalytical methods

The bioanalytical methods used were validated for the determination of:

a) Systemic exposure following Rimmyrah vs EU-Lucentis IVT administration in studies QL1205-001 and QL1205-002;

b) Anti-drug antibodies (ADA) and neutralizing anti-drug antibody (NAb) formation in human serum in the clinical studies;

c) Determination of VEGF in Human Plasma (study QL1205-001 only).

Pharmacokinetic assay- pivotal Phase 3 study

The PK assay method has been developed and validated to quantitatively detect Rimmyrah and Lucentis concentration in human serum by using electrochemiluminescence assay (ECLA).

The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results including selectivity, lower limit of quantification, the response function and calibration range (calibration curve performance), accuracy, precision, matrix effects and stability of the analyte were analysed.

The calibration range of the ECLA ranges from 30 pg/mL (LLOQ) to 20,000 pg/mL (ULOQ) QL1205/Lucentis in human serum. At least 6 assay runs with 3 replicates per run have been performed for each QC level (LLOQ, LQC, MQC, HQC and ULOQ) to asses accuracy (Bias: $\pm$20%; Bias: $\pm$25% at LLOQ and ULOQ) and precision (CV$\leq$20%; CV $\leq$25% at LLOQ and ULOQ) of the method. This is in accordance with the ICH guideline M10 on bioanalytical method validation/Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). All reported runs met the calibration curve criteria.

The quality control concentrations for Rimmyrah and Lucentis ranged from 15 pg/mL (anchor point) to 20,000 pg/mL. In total 5 QC sample concentration [30 pg/mL (LLOQ), 90 pg/mL (Low), 3,000 pg/mL (Medium), 15,000 pg/mL (High), and 20,000 pg/mL (ULOQ)] were used to assess accuracy and precision of the method.

The intra- and inter-assay accuracy and precision runs of the quality control samples for Rimmyrah and Lucentis were within the acceptance criteria for the QC-levels 90 pg/mL (Low), 3,000 pg/mL (Medium), 15,000 pg/mL (High), and 20,000 pg/mL (ULOQ). However, the intra-assay accuracy (-39.5 %) and intra-assay TE (44.2%) for the LLOQ (30 pg/ml) of Lucentis (batch VB01) did not met the acceptance criteria. In addition, one outlier by Rimmyrah (batch VB01) has also been detected for the intra-assay accuracy (-57.6%) and intra-assay TE (59.5%) for the LLOQ (30 pg/ml), but this outlier

(batch VB01) was not included in the calculation. Thus, in both Quality Control Sample Data for Rimmyrah and Lucentis in Human Serum one outlier (batch VB01) in the intra-assay (within-run) accuracy at 30 pg/mL was detected.

To confirm the bioanalytical similarity between Rimmyrah and Lucentis, accuracy and precision runs have been performed by use of both products, that met the acceptance criteria.

In addition, robustness investigations for all batches (VB01-VB06) were performed and based on the data provided, robustness appears to be demonstrated for all batches.

The selectivity was analysed using a minimum of 10 individual human serum samples of unspiked (blank) matrix and evaluated for interference. The individual blank matrices were spiked at the low end of the assay (LLOQ) and at the high end (ULOQ) of the assay.

All normal unspiked (blank) individual Rimmyrah samples were below the limit of quantification. The accuracy for all spiked Rimmyrah and Lucentis samples were within ±20% at the ULOQ of the nominal concentration. In contrast, the accuracy of 2 out of 10 spiked Rimmyrah samples and 1 out of 10 spiked Lucentis samples at the LLOQ were outside the acceptance criterion (±25%). However, as in accordance with the ICH guideline M10 on bioanalytical method validation/Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**), at least 80% of the spiked sources had an accuracy within ±25% at the LLOQ (8 out of 10 Rimmyrah samples/9 out of 10 Lucentis samples) and thus met the acceptance criteria.

No effect from lipemia on the quantification of Rimmyrah and Lucentis and no effect from haemolysis on the quantitation of Rimmyrah and Lucentis at haemolysis levels up to 20,000 pg/mL were identified. Based on the data provided, it is understood that no selectivity/matrix effect were analysed on patient serum.

For evaluating the dilutional linearity, results showed that samples diluted up to 25-fold (exclude MRD 1:2) can be quantified for Rimmyrah and Lucentis. No hook effect was observed. However, for the re-assessment only 2 dilution factors 1 and 25 has been tested (1:MRD excluded).

Specificity was performed to assess potential cross-reactivity. Specificity was evaluated by spiking blank matrix samples with varying concentrations of potential cross-reactive molecules (VEGF: 5.0, 1.0, 0.2, 0.1 and 0 ng/mL). No interference was observed for Rimmyrah at LLOQ and ULOQ level up to 5.0 ng/mL VEGF (VB27) after one run-rejection due to QCs failed (VB21). For Lucentis no interference was observed at LLOQ and ULOQ level up to 1.0 ng/mL VEGF, after two runs VB21 and VB27 were rejected due to QCs failed.

As part of validation, short-term stability of the samples (freeze-thaw (F/T) cycles and at bench top) was tested. The ranibizumab concentration in human serum was stable for 4 and 6 freeze (-60 to -80°C) and thaw [1 hour ±15 minutes (ambient temperature)] cycles. Short-term stability appears to be valid for up to six freeze/thaw cycles.

In addition, bench top stability was assessed up to 24 hours 51 minutes and 48 hours 49 minutes. For both Rimmyrah and Lucentis, bench top stability was demonstrated for at least 48 hours (VB15 and VB16), after VB13 and VB16 has failed to meet the acceptance criteria at the LQC.

Refrigerator stability of Rimmyrah assessed for 72±4 hours at 2°C to 8 °C has been demonstrated at LQC, HQC and Ultra high concentration (VB15 and VB16), after VB13 has been failed to meet acceptance criteria at LQC and HQC. Refrigerator stability of Lucentis assessed for 72±4 hours at 2°C to 8 °C has been demonstrated at LQC, HQC and Ultra high concentration (VB13 and VB16), even though one replicate at LQC has not met the acceptance criteria.

In addition, freezer stability of Rimmyrah and Lucentis when stored at -10°C to -30°C for up to 3

months was assessed in VB23, however the LQC and Ultra-high concentration samples did not meet the acceptance criteria. Therefore, two further repeats (VB25 and VB26) were analyzed and confirmed the stability of QL1205/Lucentis in Human Serum at -10°C to -30°C. Freezer stability of Rimmyrah when stored at -60°C to -80°C for up to 3 months was assessed in VB24, however the LQC stability samples did not meet the acceptance criteria. Therefore, two further repeats (VB25 and VB26) were analyzed and confirmed the stability of Rimmyrah in Human Serum at -60°C to -80°C for up to 3 months. Moreover, the stability of QL1205/Lucentis in Human Serum at -60°C to -80°C for up to 6 months was demonstrated.

Pharmacokinetic assay-supportive Phase 1

The PK assay method has been developed and validated to quantitatively detect Rimmyrah and Lucentis concentration in human serum by using electrochemiluminescence assay (ECLA).

The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results, including selectivity, lower limit of quantification, the response function and calibration range (calibration curve performance), accuracy, precision, matrix effects and stability of the analyte, were analysed.

In general, the validated and provided assay parameters (with the exception of missing selectivity/matrix effect data from patient serum and specificity in the presence of VEGF, for which accuracy was not demonstrated at LLOQ and ULOQ) met the acceptance criteria. For more detailed information about the ADA assay validation for the supportive phase 1, please refer to the D80-clinical-assessment report, section 2.1.2.1. analytical methods.

VEGF concentration assay – supportive Phase 1 Study

For the ability to exclude an interference with endogenous components, potential interference of VEGF concentrations was evaluated by fortifying and analysing Rimmyrah or Lucentis QC samples at LLOQ and ULOQ concentrations in human plasma with CTAD anticoagulation using the MSD-Based sandwich ECLA platform.

For methodological validation mainly the parallelism, accuracy, precision, selectivity in healthy individuals, selectivity in patients with AMD, specificity and stability of the analytical method were evaluated.

The quantitation range of the method was from 0.684 to 700 pg/mL with anchor points of 0.342 pg/mL and 1400 pg/mL. The back-calculated concentrations of each calibration standard were within the acceptance criteria.

To investigate the accuracy and precision of the method with the buffer QC samples at low (LQC: 2 pg/mL), medium (MQC: 30 pg/mL) and high concentrations (HQC: 525 pg/mL), a total of 6 independent analytical runs were performed. However, no accuracy and precision of the method at the LLOQ (0.684 pg/mL) and ULOQ (700 pg/mL) were performed.

The precision of matrix QC samples was investigated at low and high concentration levels (LMC and HMC). The intra- and inter-precision data were acceptable.

Sample results from other validation batches (including buffer and matrix QC samples) were analysed at LQC (2 pg/mL), LMC (3.65 pg/mL), HMC (13 pg/mL), MQC (30 pg/mL) and HQC (525 pg/mL). The mean %CV ranged between 6.1% to 18% and the mean %RE ranged between -12% to 6.0%.

The matrix recovery (selectivity) of healthy individuals and patient individuals with AMD was investigated at two concentration levels: blank matrix (Blank) and low concentration quality control (LQC 2 pg/mL VEGF), which were investigated in 6 individuals, each sample was repeated 3 times. It appears that no significant matrix effect was observed in any of the tested human plasma.

Parallelism: After regression calculation of dilution factor, the precision of the 7 biological samples ranged from 4.1% to 11.5%, and the parallelism of all samples (7/7) from all individuals (6/6) met the acceptance criteria.

The short-term stability (bench-top) investigated the stability of matrix quality control samples (LMC [3.65 pg/mL], HMC [13 pg/mL]) stored at room temperature for 24 hours or at 2°C-8°C for 24 hours. The mean %CV of all OC samples were within ±20%. The mean %RE of the HMC at ART 24 hours was -10% and at 2°C-8°C -9.2% and the mean %RE of the LMC at ART 24 hours ranged between -34.8% to -21.4% and at 2°C-8°C was -24.7%.

Freeze-thaw stability investigated the matrix quality control samples (LMC and HMC) stability that frozen at -60°C to -90°C for at least 12 hours and thawed at room temperature for at least 2 hours as a cycle; for 5 cycles. The mean %CV of all OC samples were within ±20%. The mean %RE of the HMC after 5 F/T –cycles was -9.2% and the mean %RE of the LMC after 5 F/T –cycles were measured three times (-28.2%, -7.7% and -2.7%). The freeze-thaw stability appears to be valid for up to 5 freeze/thaw cycles.

The long-term stability was investigated the stability of matrix quality control samples (LMC, HMC) stored at -10°C to -30ºC for 1 month or -60°C to -90ºC for 1, 6, 9, 12 and 15 months. The long-term stability at -10°C to -30°C for one month was demonstrated for HMC and LMC samples (mean %CV: HMC=3.9%; LMC=2.2%; mean %RE: HMC=7.7%; LMC=6.6%). The mean %CV of all OC samples were within ±20%, at -60°C to -90ºC for 1, 6, 9, 12 and 15 months. The mean %Re at -60°C to -90ºC ranged between -32.9% to 23.8% (1 month: HMC=-1.5%, LMC=-9.6%; 6 months: HMC=14.6%, LMC=23.8%; 9 months: HMC=9.2%, LMC=3.0%; 12 months: HMC=-28.8%/-14.6%, LMC=-32.9%/-20.5% and 15 months: HMC=-12.3%, LMC=-15.9%).

The specificity of this study was to investigate the specificity of the three-level test article VEGF validation samples: blank, low and high concentrations (Blank, LQC [2 pg/mL], and HQC [525 pg/mL]), adding with 0, 0.1, 1, 10, 100 ng/mL of different interfering substances Lucentis and Rimmyrah, respectively. Three replicates were tested at each concentration. The blank samples added with different concentrations of Lucentis and Rimmyrah were all BQL.

Overall, 10 ng/mL Lucentis and 1 ng/mL Rimmyrah is the highest concentration that not affect the determination of VEGF concentration in biological samples.

Anti-drug Antibody (ADA) Assay – pivotal Phase 3 study

A 3-tiered approach for the determination of anti-drug antibodies (ADA) against QL1205/Lucentis in human serum samples, using a bridging immunoassay based on MSD, compromising a screening, confirmation, and titer/quantitative stratification methods to confirm the existence of anti-Rimmyrah/ Lucentis antibodies. This strategy for immunogenicity assessment is in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1).

The following method parameters have been analysed: master-mixture interchangeability, immunogenicity equivalence, screening cut-point (SCP), confirmation cut-point (CCP), sensitivity, selectivity, system suitability samples, intra-and inter precision, specificity/cross reactivity/interference, serum sample stability (including freeze-thaw stability, processing stability, refrigerator stability and long-term stability).

Immunogenicity testing of QL1205/Lucentis was conducted by using a single assay approach with Rimmyrah (biosimilar) used as antigen. Master-mixture interchangeability experiments were used to demonstrate whether Biotin/SulfoTag-Rimmyrah and Biotin/SulfoTag- Lucentis® are equivalent and can be used interchangeably. The positive control concentrations ranged from 0 ng/mL to 5,000 ng/mL

(0, 50, 100, 2000, 500, 1000, 2000, 5000 ng/mL). Three analytical batches were analysed. Based on the provided data, for both Anti-Rimmyrah and Anti-Lucentis the mean observed response (RLU) increased with increasing positive control concentration and the intra-Master-mixture %CV as well as the Inter-Master-mixture %CV did not exceed 20%. Thus, the biotinylated/sulfo-tag labelled Rimmyrah and Lucentis are considered to be equivalent and interchangeable.

Immunogenicity equivalence was determined to demonstrate that Rimmyrah or Lucentis equally inhibited the positive control antibody signal. As positive control, 5,000 ng/mL (HPC) was used. As drug concentrations (Rimmyrah and Lucentis) 8 µg/mL, 4 µg/mL, 2 µg/mL, 1 µg/mL, 0.5 µg/mL, 0.25 µg/mL and 0 µg/mL and as master-mixture reagent pair Rimmyrah Biotin/SulfoTag were used to assess the immunogenicity equivalence. Three analytical batches were analysed. The mean observed response (RLU) decreased with increasing drug concentrations, for Anti-Rimmyrah and Anti-Lucentis respectively, and thus the inhibitory effect increased with increasing drug concentrations. The mean %inhibition was slightly higher in the Anti-Lucentis group than in the Anti-Rimmyrah group. However, the intra-Master-mixture %CV as well as intra-Master-mixture CV for inhibition was low and did not exceed 20%. In contrast, the Inter-Master-mixture %CV exceeded 20% in all 3 batches, mostly at drug concentrations above 1 µg/mL. In addition, the Inter-Master-mixture CV for % Inhibition exceeded 20% in one batch (VB06) at the drug concentrations 0.25 and 0.5 µg/mL, all other values of the Inter-Master-mixture CV for % Inhibition were below 20%. At least 2/3 batches meet the acceptance criteria (CV≤20% inhibition), and thus Rimmyrah or Lucentis appears to have an equivalent inhibitory effect on the positive signal in the master-mixture.

The normalization factor (NF) was calculated as 1.41 Ratio.

A floating screening cut point was applied as a plate specific cut point (PSCP), and it was calculated as the NC median response * NF.

The Confirmatory Cut Point (CCP) is used to distinguish the samples greater than or equal to SCP in the screening assay as the judgment data of positive samples. The confirmatory cut point was determined 35.3% inhibition rate to detect 1% false-positive rate in the confirmatory assay.

The titer cut-point (TCP) was calculated in the similar way with SCP, with 0.1% false positive rate. The normalization factor for TCP was calculated as 1.84 Ratio. A floating titer cut point was applied as a titer specific cut point (TCP), and it was calculated as the NC median response * 1.84.

The sensitivity of this method was evaluated by serial dilution of HPC to below cut point with and without drug (HPC: 5000 ng/mL; MPC: 500 ng/mL; LBC 50 ng/mL [VB07-VB32] or 25 ng/mL [VB33-VB44]).

The assay sensitivity in the absence of drug was determined as 15.20 ng/mL and in the presence of drug was determined as 19.70 ng/mL.

Intra- and inter assay precision has been assessed for NC, LPC, MPC and HPC in 6 runs, by at least two analysts on at least three different days. The assessed batches demonstrated high intra- (%CV: <10.5%) and inter- (%CV: <7.5%) assay precision of the method. The intra- and inter assay precision was considered acceptable.

The median titer of the precision-titration assay was determined as 2122.

System suitability was demonstrated for NC and PC data by a NC response of ≤ 107.4 RLU, 1.3≤LPC/NC ratio ≤ 2.2 and 99.6≤ HPC/NC ratio ≤ 212.9.

Selectivity was assessed in a minimum of 10 individual matrix of each appropriate matrix unspiked and spiked at LPC and HPC levels. No matrix effect was demonstrated neither in normal human serum samples, nor in haemolysed or lipemic samples. The signal for the spiked samples was greater than

the plate-specific cut point and confirmation cut-point of the individual samples. Only 1 un-spiked selectivity sample in the normal human serum and in haemolysed samples was above the cut point before spiking with anti-Rimmyrah positive control antibody and was therefore excluded in the final result summary.

Drug tolerance was investigated by adding different Rimmyrah concentrations (0, 100, 200, 500 and 1000 ng/mL) to different Anti-Rimmyrah Antibody (ADA) concentrations (25, 100, 200, 500, 1,000 and 2,000 ng/mL). The results showed that the PSCP (RLU) of 110.7 was exceeded at all concentrations. Thus, an ADA concentration at 25 ng/mL and up to 2000 ng/mL can tolerate drug (QL1205) concentrations up to 1000 ng/mL.

The specificity/Cross reactivity investigated the interference of the drug target VEGF. Therefore, human VEGF was added at different concentrations (0, 0.1, 0.2, 1.00 and 5.00 ng/mL). No interference was observed in 25 ng/ml of Anti-QL1205-antibody concentration at VEGF concentration up to 5.00 ng/mL. Further concentrations have not been tested.

To demonstrate the absence of a "hook' effect, the samples were prepared at concentrations above the HPC level and should generate a response greater than HPC. Anti-Rimmyrah antibody concentrations of 5,000 ng/mL, 10,000 ng/mL, 15,000 ng/mL, 20,000 ng/mL and 40,000 ng/mL were used. No Hook effect (prozone) was observed at concentrations up to 40,000 ng/mL.

In addition, freeze-thaw stability, analytical process stability and long-term storage stability of the samples has been evaluated. Freeze-thaw stability of LPC and HPC samples after at least 8 cycles of freezing (12 hours) at -60°C to -80°C and thawing at room temperature (1 hour and 15 min), were demonstrated. Bench Top stability at ambient room temperature for 25 hours and 10 minutes and refrigerator stability for at least 73 hours and 2 minutes at 2°C to 8°C were shown. In addition, long-term stability of the samples for at least 95 days at -60°C to – 90°C / -10 °C to -30°C were verified.

Anti-drug Antibody (ADA) Assay – supportive Phase 1 study

A 3-tiered approach for the determination of anti-drug antibodies (ADA) against QL1205/Lucentis in human serum samples, using an Immunodepletion-bridging Electrochemiluminescence Assay (IMD-B ECLIA) based on MSD, compromising a screening, confirmation, and titer/quantitative stratification methods to confirm the existence of anti-Rimmyrah/ Lucentis antibodies. This strategy for immunogenicity assessment is in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1).

Following method parameters has been analysed: capture reagent/assay reagent interchangeability, immunosuppression equivalence, screening threshold (SCP), confirmation threshold (CCP), method range and Hook effect, sensitivity, specificity, selectivity, system suitability samples and precision, method robustness, serum sample stability (including freeze-thaw stability, processing stability, and long-term stability).

In general, the validated and provided assay parameters (with the exception of missing selectivity data in haemolytic or lipemic samples) met the acceptance criteria. For more detailed information about the ADA assay validation for the supportive phase 1, please refer to the D80-clinical-assessment report, section 2.1.2.1. analytical methods.

Neutralizing antibody (NAb) assay – pivotal phase 3 study

A competitive ligand binding assay (CLBA) has been developed and validated based on MSD Platform by Covance for determination of neutralising anti-dug antibodies (NAb) in human serum samples.

The method was validated with an appropriate number of human serum samples (a run size of up to 48 samples; results from 31 analytical runs).

Following method parameters has been analysed: master-mixture interchangeability, immunogenicity equivalence, screening cut-point (SCP), sensitivity, intra- and inter- precision, system suitability, selectivity, specificity/interference, drug tolerance and hook effect as well as serum sample stability (including freeze-thaw stability, bench top stability, refrigerator stability and long-term stability).

Master-mixture interchangeability experiments were used to demonstrate whether Biotin/SulfoTag labelled Rimmyrah and Biotin/SulfoTag labelled Lucentis are equivalent and can be used interchangeably. The positive control concentrations ranged from 0 ng/mL to 2,000 ng/mL (0, 100, 200, 500, 1,000, 2,000 ng/mL). Three analytical batches (VB01, VB02 and VB04) were analysed. Based on the provided data, for both Anti-Rimmyrah and Anti-Lucentis the mean observed response (RLU) decreased with increasing positive control (PC) concentration. Therefore, the higher the PC concentration, the higher the Inhibition %. In addition, the intra-Master-mixture %CV as well as the Inter-Master-mixture %CV did not exceed 20%. Thus, the biotinylated/sulfo-tag labelled Rimmyrah and Lucentis are considered to be equivalent and interchangeable.

Immunogenicity equivalence was used to demonstrate that Rimmyrah or Lucentis equally inhibited the positive control antibody signal. As positive control, 2000 ng/mL (HPC) was used. As drug concentrations (Rimmyrah and Lucentis) 8 µg/mL, 4 µg/mL, 2 µg/mL, 1 µg/mL, 0.5 µg/mL, 0.25 µg/mL and 0 µg/mL and as master-mixture reagent Biotin/SulfoTag labelled Rimmyrah were used to assess the immunogenicity equivalence. Three analytical batches were analysed (VB03, VB05 and VB06). The intra-Master-mixture %CV did not exceed 20%, except for one value (32.5%, Batch VB03, drug concentration 2000 ng/mL). However, this is considered acceptable. The Inter-Master-mixture %CV was below 20% for all drug concentrations. Based on the results provided QL1205/Lucentis appears to have an equivalent inhibitory effect on the positive signal in the master-mixture.

For the determination of the Screening Cut Point a minimum but appropriate number of human serum samples (approx. 30 individual matrix samples) were tested on 2 different days by at least two analysts.

The normalization factor (NF) was calculated as 78.25%.

A floating screening cut point was applied as a plate specific cut point (PSCP), and it was calculated as the NC median response * NF.

The LPC Concentration Determination and Assay Sensitivity of this method was evaluated by serial dilution of HPC to below cut point. The LPC concentration was determined as 99.90 ng/mL but final determined as 100 ng/mL. The assay sensitivity in the absence of drug was determined as 85.50 ng/mL.

Intra- and inter- assay precision has been assessed for NC, LPC, MPC and HPC in 6 runs, by at least two analysts on at least three different days. The assessed batches demonstrated intra- (%CV: ≤17.9%) and inter- (%CV: ≤13.4%) assay precision of the method. The intra- and inter assay precision was considered acceptable.

System suitability was demonstrated for NC, LPC (100 ng/mL) and HPC (2000 ng/mL). NC response of ≥ 1243.1 RLU, 47.14≤ LPC ratio⩽84.31 and HPC ratio ≤ 26.18 has been determined.

Selectivity was assessed in a minimum of 10 individual matrix of each appropriate matrix unspiked and spiked at LPC and HPC levels in normal human serum. In addition, a minimum of 5 individual (or 5 pooled) haemolysed or lipemic samples of appropriate matrix unspiked and spiked at LPC and HPC levels were evaluated. No matrix effect was observed neither in normal human serum samples, nor in haemolysed or lipemic samples.

The specificity investigated the interference of the drug target VEGF. Therefore, human VEGF were added at different concentrations (0, 0.1, 0.2, 1 and 5 ng/mL). Anti-Drug-Rimmyrah was used at concentrations of 100, 200, 500, 1,000, 2,000 ng/mL. The interference was assessed in one batch (VB27). No interference was observed in up to 2,000 ng/mL of Anti-QL1205-antibody concentration at VEGF concentration up to 5 ng/mL. Further concentrations have not been tested.

Drug tolerance were investigated by adding different Rimmyrah concentrations (0, 10, 20, 50 and 100 ng/mL) to various Anti-Rimmyrah neutralizing antibody concentrations (100, 200, 500, 1,000 and 2,000 ng/mL). Based on the provided data, the Anti-Rimmyrah neutralizing antibody concentration at 2000-100 ng/mL can be detected in the presence of 100 ng/mL drug (QL1205).

To demonstrate the absence of a "hook' effect, the samples were prepared at concentrations above the HPC level and should generate a response lower than HPC. Anti-Rimmyrah antibody concentrations of 50,000 ng/mL, 20,000 ng/mL, 15,000 ng/mL, 10,000 ng/mL, 5,000ng/mL and 3,000 ng/mL were used. No Hook effect (prozone) was observed at concentrations up to 50,000 ng/mL.

In addition, freeze-thaw stability, bench top stability, refrigerator stability and long-term storage stability of the samples has been evaluated. Freeze-thaw stability of LPC and HPC samples after 6 and 8 cycles of freezing (12 hours) at -60°C to -80°C and thawing at room temperature (1 hour and 15 min), were demonstrated. Bench Top stability at ambient room temperature for 23 hours and 47 minutes and refrigerator stability for at least 72 hours and 18 minutes at 2°C to 8°C were shown. However, baseline stability samples failed to meet the acceptance criteria at LPC and HPC in short term stability (F/T, Bench top and RS stability) of VB25. The applicant explained that the baseline samples were used for information monitoring the trend and that the baseline results has no impact to the stability results.

In addition, long-term stability of the samples for at least 93 days at -60°C to – 90°C / -10 °C to -30°C were verified.

Neutralizing antibody (NAb) assay – supportive phase 1 study

A competitive ligand binding assay (CLBA) has been developed and validated based on MSD Platform by United-Power Pharma Tech Co., Ltd. for determination of neutralising antibodies (NAb) against Rimmyrah and Lucentis monoclonal antibodies in human serum samples.

Following method parameters has been analysed: interchangeability, method threshold (ACP), sensitivity, intra- and inter- precision, system suitability, selectivity, specificity, drug tolerance and hook effect as well as serum sample stability (including freeze-thaw stability, bench top stability, refrigerator stability and long-term stability).

The assay parameters validated and provided met the acceptance criteria. For more detailed information about the Nab-assay validation for the supportive phase 1, please refer to the D80-clinical-assessment report, section 2.1.2.1. analytical methods.

2.4.3. Clinical pharmacology studies

Introduction

Clinical Phase 3 Study QL1205-002

The Phase 3 study, Study QL1205-002, was a randomised, double-masked, parallel group, multicenter study to compare the efficacy, safety, pharmacokinetics and immunogenicity between Rimmyrah and Lucentis in subjects with wAMD. At least 580 subjects will be enrolled and randomized in a 1:1 ratio to

receive either the reference product Lucentis® (0.05 mL of 10 mg/mL ranibizumab) or the investigational product (IP) Rimmyrah (0.05 mL of 10 mg/mL ranibizumab) in the study eye once every 4 weeks for 48 weeks. Subjects will be randomized by interactive web response system (IWRS) to receive 13 doses of either Rimmyrah or Lucentis® in the study eye.

PK analysis was performed in a subset of 73 subjects, including 33 subjects for Rimmyrah and 40 subjects for Lucentis. The systemic concentration of ranibizumab were obtained pre-first dose, at 22 hours after first dose and after the sixth dose (administered at Week 20). Summary statistics are used to describe the PK profile of QL1205/Lucentis. Individual and mean serum concentration values over time are presented on a linear scale. Descriptive statistics (arithmetic and geometric mean, SD, coefficient of variation [CV], minimum, maximum, and median) of the serum concentrations versus time are also presented.

Immunogenicity (anti-ranibizumab antibodies, antidrug antibody [ADA], and neutralizing ADA [NAb]) measurements were performed before treatment at Day 1, Week 4, Week 8, Week 12, Week 24, and Week 52. Additional samples for monitoring of immunogenicity were collected from subjects with any signs of intraocular inflammation, as these might indicate an immune reaction. The incidence of ADAs and NAb are summarized for the SAF using frequency of ADA-positive and NAb-positive (if available) samples for each time point and overall, for each treatment arm separately. The actual frequency for each treatment arm is descriptively presented using n (%) and a 95% Clopper-Pearson CI. The overall incidence of treatment-induced and treatment-boosted ADAs is also calculated and presented by treatment and visit.

Supportive Study QL1205-001

The Phase 1 study, Study QL1205-001, was a randomised, double-blinded, parallel-group, active-controlled Phase 1 study to compare the safety, PK, and PD of Rimmyrah and Lucentis (China) in patients with neovascular (wet) age-related macular degeneration (wAMD). Each subject was administered Rimmyrah or Lucentis 0.5 mg (0.05 mL) via IVT injection on Day 1, 29 and 57. This trial was a safety exploratory trial. Exploratory analysis on efficacy and PK was performed. There was no specific statistical hypothesis. All 48 screened eligible subjects were randomized 1:1 to study treatment (Experimental: Control).

The results were presented, including the number of subjects, arithmetic mean, minimum, maximum, median, standard deviation, and the geometric mean of the concentration of ranibizumab in each group. The pharmacokinetic parameters mainly include Cmax, AUC0-t, AUC0-Infinity. They were used for ANOVA analysis after logarithmic conversion. Tmax were presented as their number, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

Study results

Pharmacokinetic results of PK-Subgroup Analysis of the pivotal clinical Phase 3 Study QL1205-002

PK analysis was performed in a subset of 73 subjects, including 33 subjects for Rimmyrah and 40 subjects for Lucentis. The serum levels of ranibizumab were evaluated at baseline (before treatment), on Day 2 (22 hours after the first dose), and at steady-state at Week 20 (22 hours after the sixth dose) at expected Tmax (0.9 days).

Table 3. Serum Concentration – Summary Statistics – Pharmacokinetics Set

Visit	PK Profile	Statistic	QL1205 (N=33)	Lucentis (N=40)	
Day 1	Serum concentration (pg/mL)	n	32	37	
		Mean (SD)	544.622 (2998.6985)	491.596 (2505.7163)	
		CV%	550.6	509.7	
		Median	0.000	0.000	
		Min, Max	0.00, 16975.34	0.00, 15187.38	
		GeoMean (GeoCV%)	409.697 (2970.6)	389.504 (880.9)	
		GeoRatio (95% CI)			105.2 (4.2 – 2643.6)
Day 2	Serum concentration (pg/mL)	n	31	38	
		Mean (SD)	2599.361 (2732.8828)	2799.192 (3387.9295)	
		CV%	105.1	121.0	
		Median	1916.260	1751.985	
		Min, Max	0.00, 14317.86	0.00, 19464.09	
		GeoMean (GeoCV%)	1907.958 (105.5)	1910.067 (114.3)	
		GeoRatio (95% CI)			99.9 (64.5 – 154.8)
Week 20	Serum concentration (pg/mL)	n	28	32	
		Mean (SD)	2642.274 (2981.4767)	2730.374 (2907.0089)	
		CV%	112.8	106.5	
		Median	1988.720	2106.855	
		Min, Max	49.02, 15574.87	70.55, 15728.15	
		GeoMean (GeoCV%)	1435.013 (237.7)	1741.314 (150.3)	
		GeoRatio (95% CI)			82.4 (43.6 – 155.9)

a. Abbreviations: CI, confidence interval; CV, coefficient of variation; GeoCV%, Geometric per cent coefficient of variation; GeoMean, Geometric Mean; GeoRatio, Geometric Ratio; Max, Maximum; Min, Minimum; N, number of subjects; n, number of subjects in a specified category; PK, pharmacokinetics; SD, standard deviation.
b. Note: Day 1 – PK blood samples were collected ≤60 minutes before the first intravitreal injection of study treatment (QL1205/Lucentis).
c. Day 2 – PK blood samples were collected 22 hours (±10 minutes) after the Day 1 (first) intravitreal injection of study treatment (QL1205/Lucentis).
d. Week 20 – PK blood samples were collected 22 hours (±10 minutes) after the sixth dose of study treatment (QL1205/Lucentis).
e. Subjects POL02-0792 and POL02-0796 took bevacizumab prior to Week 20. Therefore, data for Week 20 are excluded.
f. Source: Study QL1205-002 CSR Table 14.2.2.4.1.1

Pharmacokinetic results of the supportive clinical Phase 1 Study QL1205-001

The PK population included all subjects who were randomised and had received a single dose of the investigational product (IP) with evaluable PK parameters and without any major protocol deviation to interfere with the absorption, distribution, metabolism and excretion of the compounds to be measured.

The PK blood samples were collected as follows: 0h (D1, before the first administration), 3h after administration (D1), 24h (D2), 48h, 96h, 168h, 336h, 504h, D29 (before the second administration), D57 (before the third administration), D85, and D113. There were 12 blood sample collection points in total, collecting approximately 3mL of venous blood each time, which was used to detect the drug

concentration of ranibizumab in serum. The pharmacokinetic parameters mainly include C_{max}, AUC0-t, and $AUC_{0\text{-Infinity}}$.

Table 4. Results of Main PK Parameters (PKAS)

Parameter (Unit)	N	QL1205 Group Geometric Mean	Lucentis Group Geometric Mean	Geometric Mean Ratio and 90% CI (QL1205/Lucentis Group)	F	P
$AUC_{0\text{-}t}$ (h*pg/mL)	46	508449.96	484873.19	104.86% (87.81%, 125.23%)	0.20	0.655
$AUC_{0\text{-}\infty}$ (h*pg/mL)	46	621974.82	557142.19	111.64% (90.83%, 137.20%)	0.80	0.375
C_{max} (pg/mL)	46	2586.73	3102.94	83.36% (54.90%, 126.60%)	0.54	0.468

Note: The variance analysis of the natural logarithms of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} was performed. The model considers treatment arm as a fixed effect.

Table 5. Pharmacokinetic Parameters in the Rimmyrah Treatment Group (PKAS)

	$t_{1/2}$ (h)	λ_z (h^{-1})	C_{max} (pg/mL)	V_d (mL)	$AUC_{0\text{-}t}$ (h*pg/mL)	$AUC_{0\text{-}\infty}$ (h*pg/mL)	MRT (h)	CL (mL/h)	T_{max} (h)
N	22	22	22	22	22	22	22	22	22
Mean	642.71	0.0018	4538.00	1293149.63	556810.43	695257.02	646.7150	1388.40	20.05
SD	456.52	0.0017	7599.14	1131010.43	300213.80	390426.27	369.7060	422.83	27.33
CV%	71.03	95.9602	167.46	87.46	53.92	56.16	57.1668	30.45	136.28
Median	577.27	0.0012	2115.00	1024259.10	470651.08	584497.27	663.6968	1400.09	3.06
Max	2304.72	0.0067	35400.00	5342066.28	1712157.08	2063389.29	1412.4894	2220.93	95.28
Min	102.78	0.0003	706.00	200587.07	268930.34	278998.40	151.7815	417.14	2.85
Geomean	516.95	0.0013	2586.73	982011.32	508449.96	621974.82	532.3523	1316.72	8.98
Geomean CV%	81.79	81.7888	111.77	88.17	41.87	48.38	77.3049	36.86	208.63
(Q1, Q3)									(3.00, 24.00)

Data Source: Listing 14.2.7.3

Table 6. Pharmacokinetic Parameters in the Lucentis Treatment Group (PKAS)

	$t_{1/2}$ (h)	λ_z (h^{-1})	C_{max} (pg/mL)	V_d (mL)	AUC_{0-t} (h*pg/mL)	$AUC_{0-\infty}$ (h*pg/mL)	MRT (h)	CL (mL/h)	T_{max} (h)
N	24	24	24	24	24	24	24	24	24
Mean	437.94	0.0032	4472.83	827270.66	507521.40	594139.05	482.73	1326.56	19.58
SD	248.17	0.0036	5108.98	541756.95	156398.65	216439.29	306.44	336.86	23.52
CV%	56.67	112.2900	114.22	65.49	30.82	36.43	63.48	25.39	120.16
Median	493.26	0.0014	2375.00	872572.01	452654.19	564912.14	476.68	1361.81	3.03
Max	794.50	0.0152	23800.00	2405365.95	899530.71	1150209.21	1082.09	2204.78	96.00
Min	45.48	0.0009	918.00	94656.01	223094.12	228343.68	64.51	839.75	2.85
Geomean	334.91	0.0021	3102.94	622190.09	484873.19	557142.19	369.45	1287.70	9.21

	$t_{1/2}$ (h)	λ_z (h^{-1})	C_{max} (pg/mL)	V_d (mL)	AUC_{0-t} (h*pg/mL)	$AUC_{0-\infty}$ (h*pg/mL)	MRT (h)	CL (mL/h)	T_{max} (h)
Geomean CV%	106.57	106.5692	92.43	107.11	32.02	38.57	100.06	25.26	207.76
(Q1, Q3)									(3.00, 24.00)

Data Source: Listing 14.2.7.4

2.4.3.1. Pharmacodynamics

No PD similarity of Rimmyrah and Lucentis has been performed in the pivotal clinical phase 3 study (QL1205-002). However, PD similarity of Rimmyrah and Lucentis in terms of VEGF inhibition has been investigated as part of the supportive phase 1 study (QL1205-001).

The mode of action of ranibizumab is established. Pharmacodynamics (PD) similarity of Rimmyrah and Lucentis® with respect to biological activity, has been evaluated in nonclinical in vitro studies (e.g. in vitro functional characterisation and analytical comparability). For further information and evaluation please refer to the Section 3.2. Non-clinical aspects for a final summary and overall conclusion.

In addition, the applicant has not performed studies on dose-response and dose finding or on genetic difference in PD response. Since this is a biosimilar development, this is acceptable and studies in these aspects are not required.

In the clinical study QL1205-002, the change in CFT at Week 2, Week 4, Week 8, Week 16, Week 24, and Week 52 compared to the Baseline in the study eye was defined as secondary endpoints, which addresses the pharmacodynamic aspect of ranibizumab. Similarity in clinical efficacy was assessed in the pivotal efficacy study (see efficacy section).

Primary pharmacology

Immunogenicity in the Clinical Phase 3 Study QL1205-002

In the Phase 3 study with wAMD subjects, the immunogenicity profile was evaluated as one of the secondary endpoints regarding the incidence of ADA and NAbs. The incidence and titre of ADA and the incidence of NAbs were assessed for both Rimmyrah and Lucentis treatment groups. Blood samples for determination of immunogenicity were collected at 6-time points during the test period, before dose administration on Day 1 (Baseline), Week 4, 8, 12, 24 and 52.

In general, a similar number of ADA positive patients was observed at baseline (Day1) and at the post-treatment time points (week 4, 8, 12, 24 and 52). Based on the safety set, 294 patients out of 309 patients in the Rimmyrah treatment group, provided blood samples for the pre-treatment ADA assessment. 12 (4.1%) of 294 patients were ADA positive at pre-treatment (day 1). In the Lucentis

treatment group, 295 patients out of 307 patients provided blood samples for the pre-treatment ADA assessment. 11 (3.7%) of these 295 patients were ADA positive at pre-treatment (day 1). In total 27 patients out of 309 patients in the Rimmyrah treatment group (8.7%) and 28 patients out of 307 patients in the Lucentis group (9.1%) were detected ADA positive during the study up to week 52. Thereof, two patient in the Rimmyrah group (2/27 [7.4%]) and three patients in the Lucentis group (3/28 [10.7%)] had neutralizing antibodies during the study up to week 52.

A slight increase of ADA positivity was observed from baseline to week 24 in both treatment groups. In the post-treatment detection of ADAs until week24, ADAs were detected in 12-15 participants (4.4%-5.6%) in the Rimmyrah treatment group and in 15-18 participants (5.4%-6.8%) in the Lucentis group. However, the detected proportion of subjects who were ADA positive at any time point was low (approximately 4% to 7%) until week 52 and were similar between both treatment groups (QL1205: 4.1%-5.6%; Lucentis 3.7%-6.8%).

Table 7. Immunogenicity: Summary by Visit – Safety Set

Test Name	Visit	Statistic	QL1205 (N=309)	Lucentis (N=307)
ADA positive	During study up to Week 8	N evaluable	308	307
		n (%)	20 (6.5)	18 (5.9)
		95% CI	4.0 – 9.9	3.5 – 9.1
ADA positive	During study up to Week 52	N evaluable	309	307
		n (%)	27 (8.7)	28 (9.1)
		95% CI	5.8 – 12.5	6.1 – 12.9
ADA positive	Day 1	N evaluable	294	297
		n (%)	12 (4.1)	11 (3.7)
		95% CI	2.1 – 7.0	1.9 – 6.5
ADA positive	Week 4	N evaluable	288	294
		n (%)	16 (5.6)	17 (5.8)
		95% CI	3.2 – 8.9	3.4 – 9.1
ADA positive	Week 8	N evaluable	278	280
		n (%)	15 (5.4)	15 (5.4)
		95% CI	3.1 – 8.7	3.0 – 8.7
ADA positive	Week 12	N evaluable	274	276
		n (%)	12 (4.4)	18 (6.5)
		95% CI	2.3 – 7.5	3.9 – 10.1
ADA positive	Week 24	N evaluable	270	266
		n (%)	15 (5.6)	18 (6.8)
		95% CI	3.1 – 9.0	4.1 – 10.5
ADA positive	Week 52	N evaluable	275	267
		n (%)	10 (3.6)	17 (6.4)
		95% CI	1.8 – 6.6	3.8 – 10.0
Frequency of NAb	During study up to Week 8	N evaluable	20	18
		n (%)	1 (5.0)	2 (11.1)
		95% CI	0.1 – 24.9	1.4 – 34.7
Frequency of NAb	During study up to Week 52	N evaluable	27	28
		n (%)	2 (7.4)	3 (10.7)
		95% CI	0.9 – 24.3	2.3 – 28.2
Frequency of NAb	Day 1	N evaluable	12	11
		n (%)	0	0
		95% CI	0.0 – 26.5	0.0 – 28.5
Frequency of NAb	Week 4	N evaluable	16	17
		n (%)	0	2 (11.8)
		95% CI	0.0 – 20.6	1.5 – 36.4
Frequency of NAb	Week 8	N evaluable	15	15
		n (%)	1 (6.7)	0
		95% CI	0.2 – 31.9	0.0 – 21.8
Frequency of NAb	Week 12	N evaluable	12	18
		n (%)	0	0
		95% CI	0.0 – 26.5	0.0 – 18.5
Frequency of NAb	Week 24	N evaluable	15	18
		n (%)	1 (6.7)	1 (5.6)
		95% CI	0.2 – 31.9	0.1 – 27.3
Frequency of NAb	Week 52	N evaluable	10	17
		n (%)	0	1 (5.9)
		95% CI	0.0 – 30.8	0.1 – 28.7

Abbreviations: ADA, antidrug antibody; N, number of subjects; n, number of subjects at the specified time point; NAb, neutralizing antibody.
Note: 95% CIs were constructed using the Clopper-Pearson method.
Source: Table 14.3.4.1.3.1

Table 8. Immunogenicity: Summary of Treatment-Induced Antidrug Antibodies by Visit – Safety Set

Test Name	Visit	Statistic	QL1205 (N=309)	Lucentis (N=307)
Treatment-Induced ADA	ADA positive at least once after baseline to Week 8	N evaluable	286	288
		n (%)	7 (2.4)	6 (2.1)
		95% CI	1.0 – 5.0	0.8 – 4.5
Treatment-Induced ADA	ADA positive at least once after baseline to Week 52	N evaluable	294	290
		n (%)	12 (4.1)	16 (5.5)
		95% CI	2.1 – 7.0	3.2 – 8.8
Treatment-Induced ADA	Week 4	N evaluable	275	284
		n (%)	4 (1.5)	6 (2.1)
		95% CI	0.4 – 3.7	0.8 – 4.5
Treatment-Induced ADA	Week 8	N evaluable	269	272
		n (%)	6 (2.2)	5 (1.8)
		95% CI	0.8 – 4.8	0.6 – 4.2
Treatment-Induced ADA	Week 12	N evaluable	265	268
		n (%)	2 (0.8)	9 (3.4)
		95% CI	0.1 – 2.7	1.5 – 6.3
Treatment-Induced ADA	Week 24	N evaluable	256	256
		n (%)	4 (1.6)	9 (3.5)
		95% CI	0.4 – 4.0	1.6 – 6.6
Treatment-Induced ADA	Week 52	N evaluable	263	257
		n (%)	4 (1.5)	12 (4.7)
		95% CI	0.4 – 3.8	2.4 – 8.0
Treatment-Induced NAb	NAb positive at least once after baseline to Week 8	N evaluable	11	10
		n (%)	0	1 (10.0)
		95% CI	0.0 – 28.5	0.3 – 44.5
Treatment Induced NAb	NAb positive at least once after baseline to Week 52	N evaluable	11	10
		n (%)	1 (9.1)	1 (10.0)
		95% CI	0.2 – 41.3	0.3 – 44.5
Treatment-Induced NAb	Week 4	N evaluable	11	10
		n (%)	0	1 (10.0)
		95% CI	0.0 – 28.5	0.3 – 44.5
Treatment-Induced NAb	Week 8	N evaluable	8	9
		n (%)	0	0
		95% CI	0.0 – 36.9	0.0 – 33.6
Treatment-Induced NAb	Week 12	N evaluable	8	8
		n (%)	0	0
		95% CI	0.0 – 36.9	0.0 – 36.9
Treatment-Induced NAb	Week 24	N evaluable	8	8
		n (%)	1 (12.5)	1 (12.5)
		95% CI	0.3 – 52.7	0.3 – 52.7
Treatment-Induced NAb	Week 52	N evaluable	6	5
		n (%)	0	0
		95% CI	0.0 – 45.9	0.0 – 52.2

Abbreviations: ADA, antidrug antibody; N, number of subjects; n, number of subjects at the specified time point; NAb, neutralizing antibody.
Note: 95% CIs were constructed using the Clopper-Pearson method.
Source: Table 14.3.4.1.3.2

Effect of ADAs on efficacy endpoints

- *BCVA at Week 8 by ADA result:*

Analyses of the main estimand for the BCVA at Week 8 by ADA result (positive/negative up to Week 8) was provided for the ITT Set (Table 9, below) and PP Set (Table 10, below). In total, 38 subjects (QL1205: 20 subjects; Lucentis: 18 subjects) were tested ADA positive in the ITT set.

Table 9. Primary Outcome – Main Estimand – Best Corrected Visual Acuity, Analysis at Week 8 – by Antidrug Antibody Result – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
ADA negative up to Week 8						
QL1205	287	6.52	0.577	(5.39, 7.65)	(5.57, 7.47)	
Lucentis	290	7.08	0.573	(5.96, 8.20)	(6.14, 8.02)	
QL1205 – Lucentis		-0.56	0.735	(-2.00, 0.88)	(-1.77, 0.65)	0.4435
ADA positive up to Week 8						
QL1205	20	0.86	2.324	(-3.70, 5.41)	(-2.97, 4.68)	
Lucentis	18	8.09	2.587	(3.02, 13.16)	(3.84, 12.35)	
QL1205 – Lucentis		-7.24	3.145	(-13.40, -1.07)	(-12.41, -2.06)	0.0214

Abbreviations: ADA, antidrug antibody; BCVA, best corrected visual acuity; ITT, Intent-to-Treat; n, number of subjects in the specified category.
Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm. Dependent variable was the change of BCVA letters from Baseline in the study eye. Equivalence was declared if the difference between the 2 treatment groups was within the range [-3.49, +3.49] letters.
Source: Table 30 (Table 14.2.1.1.27) of the final updated QL1205-002 CSR

Table 10. Primary Outcome – Main Estimand – Best Corrected Visual Acuity, Analysis at Week 8 – by Antidrug Antibody Result – Per Protocol Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
ADA negative up to Week 8						
QL1205	266	6.81	0.589	(5.65, 7.96)	(5.84, 7.78)	
Lucentis	268	7.29	0.582	(6.15, 8.43)	(6.33, 8.25)	
QL1205 – Lucentis		-0.48	0.745	(-1.94, 0.98)	(-1.71, 0.75)	0.5198
ADA positive up to Week 8						
QL1205	18	1.07	2.457	(-3.74, 5.89)	(-2.97, 5.11)	
Lucentis	16	6.91	2.844	(1.34, 12.49)	(2.24, 11.59)	
QL1205 – Lucentis		-5.84	3.465	(-12.63, 0.95)	(-11.54, -0.14)	0.0918

Abbreviations: ADA, antidrug antibody; BCVA, best corrected visual acuity; ITT, Intent-to-Treat; n, number of subjects in the specified category.
Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm. Dependent variable was the change of BCVA letters from Baseline in the study eye. Equivalence was declared if the difference between the 2 treatment groups was within the range [-3.49, +3.49] letters.
Source: Table 31 (Table 14.2.1.1.28) of the final updated QL1205-002 CSR

In the ITT population, a mean change from baseline BCVA at Week 8 of 6.52 ETDRS letters (95% CI: 5.39, 7.65) was reached for Rimmyrah and of 7.08 ETDRS letters for Lucentis (95% CI: 5.96, 8.20) in ADA negative patients. Therefore, biosimilarity was concluded in ADA negative patients, since the 95% CI of the adjusted treatment difference of -0.56 ETDRS letters was [-2.00, 0.88], which was completely contained within the predefined equivalence margin of ±3.49 letters. However, significant differences were shown for the ADA positive subjects ($p < 0.05$). The 95% CI of the adjusted treatment difference of -7.24 ETDRS letters was [-13.40, -1.07], which was not contained within the predefined equivalence margin of ±3.49 letters.

In the PP set 34 subjects (QL1205: 18 subjects; Lucentis: 16 subjects) were tested ADA positive. No significant differences between Rimmyrah and Lucentis were reported for both ADA negative and ADA positive patients, respectively. However, for ADA positive patients the 95% CI of the adjusted treatment difference of -5.84 ETDRS letters [-12.63, 0.95] was not contained within the predefined equivalence margin of ±3.49 letters.

- *CFT at Week 4 and at Week 8 by ADA result:*

Analyses for CFT at Week 4 in both the ITT (38 subjects; QL1205: 20 subjects; Lucentis: 18 subjects) and PP Sets (34 subjects; QL1205: 18 subjects; Lucentis: 16 subjects) for the main estimand by ADA status were provided in the following tables, Table 11 and Table 12 respectively. Analyses for CFT at Week 8 in the ITT Set was provided in Table 13.

Table 11. Secondary Outcome – Main Estimand – Central Foveal Thickness (µm), Analysis at Week 4 – by Antidrug Antibody Result – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
ADA negative						
QL1205	287	-80.6	6.64	(-93.6, -67.6)	(-91.5, -69.7)	
Lucentis	290	-89.2	6.54	(-102.0, -76.4)	(-99.9, -78.4)	
QL1205 – Lucentis		8.6	8.43	(-7.9, 25.1)	(-5.3, 22.5)	0.3089
ADA positive						
QL1205	20	-48.9	32.07	(-111.8, 13.9)	(-101.7, 3.8)	
Lucentis	18	-118.3	35.70	(-188.3, -48.4)	(-177.1, -59.6)	
QL1205 – Lucentis		69.4	43.38	(-15.6, 154.5)	(-1.9, 140.8)	0.1095

Abbreviations: ADA, antidrug antibody; ITT, Intent-to-Treat; n, number of subjects in the specified category.
Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm. Dependent variable was the change in central foveal thickness from Baseline in the study eye.
Source: Table 39 (Table 14.2.2.3.16) of the final updated QL1205-002 CSR

Table 12. Secondary Outcome – Main Estimand – Central Foveal Thickness (µm), Analysis at Week 4 – by Antidrug Antibody Result – Per Protocol Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
ADA negative up to Week 8						
QL1205	266	-81.0	6.78	(-94.3, -67.7)	(-92.2, -69.9)	
Lucentis	268	-91.4	6.68	(-104.5, -78.3)	(-102.4, -80.5)	
QL1205 – Lucentis		10.4	8.57	(-6.4, 27.2)	(-3.7, 24.5)	0.2240
ADA positive up to Week 8						
QL1205	18	-48.8	32.92	(-113.4, 15.7)	(-103.0, 5.3)	
Lucentis	16	-130.8	38.13	(-205.5, -56.1)	(-193.5, -68.1)	
QL1205 – Lucentis		82.0	46.43	(-9.0, 173.0)	(5.6, 158.3)	0.0775

Abbreviations: ADA, antidrug antibody; ITT, Intent-to-Treat; n, number of subjects in the specified category.
Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm. Dependent variable was the change in central foveal thickness from Baseline in the study eye.
Source: Table 40 (Table 14.2.2.3.17) of the final updated QL1205-002 CSR

Table 13. Secondary Outcome – Main Estimand – CFT (µm), Analysis at Week 8 – by ADA Result – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
ADA negative						
QL1205	287	-92.8	7.19	(-106.9, -78.7)	(-104.6, -81.0)	
Lucentis	290	-99.5	7.13	(-113.5, -85.6)	(-111.3, -87.8)	
QL1205 – Lucentis		6.8	9.15	(-11.2, 24.7)	(-8.3, 21.8)	0.4606
ADA positive						
QL1205	20	-83.6	33.17	(-148.6, -18.6)	(-138.1, -29.0)	
Lucentis	18	-124.9	36.91	(-197.3, -52.6)	(-185.6, -64.2)	
QL1205 – Lucentis		41.4	44.89	(-46.6, 129.3)	(-32.5, 115.2)	0.3568

Abbreviations: ADA, antidrug antibody; ITT, Intent-to-Treat; n, number of subjects in the specified category.
Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm. Dependent variable was the change in central foveal thickness from Baseline in the study eye.
Source: Table 14.2.2.3.19 of the final updated QL1205-002 CSR

For the change in CFT compared to baseline in the study eye, there was a trend of decrease for both treatment arms independent of the ADA status, with no statistically significant differences between the groups at Week 4 and Week 8. At Week 4, the mean CFT changes from baseline in ADA negative patients were -80.6 µm (95% CI: -93.6, -67.6) and -89.2 µm (95% CI: -102.0, -76.4) in the Rimmyrah and Lucentis groups, respectively, whereas in ADA positive patients the mean CFT changes from baseline were -48.9 µm (95% CI: -111.8, 13.9) and -118.3 µm (95% CI: -188.3, -48.4) in the Rimmyrah and Lucentis groups, respectively. At Week 8, the mean CFT values were -92.8 (95% CI: -106.9, -78.7) for Rimmyrah and -99.5 (95%CI: -113.5; -85.6) for Lucentis in ADA negative patients and -83.6 (95% CI: -148.6, -18.6) for Rimmyrah and -124.9 (95%CI: -197.3, -52.6) in ADA positive patients.

Impact of ADAs on clinical safety

Based on the limited data available, no TEAE of drug hypersensitivity, anaphylaxis or intraocular inflammation, was reported in ADA positive patients, neither for the Rimmyrah nor for the Lucentis group. In general, the number of patients with at least one TEAE in the overall safety data set was similar between Rimmyrah and Lucentis for ADA negative patients (QL1205: n=204 [72.3%] vs Lucentis: n=198 [71%]), whereas a slightly difference was observed in the ADA positive patients (QL1205: n=22 [81.5%] vs. Lucentis: n=20 [71.4%]). However, the numerical differences were very small, no TEAE was reported more than twice and no new safety signal or major safety concern have been identified in ADA positive patients.

Immunogenicity in the Clinical Phase 1 Study QL1205-001

48 wAMD subjects were enrolled and randomised in the clinical Phase 1 study QL1205-001, with 23 subjects for Rimmyrah and 25 for Lucentis. Blood samples for determination of immunogenicity were collected at 0h (before the first dose), D1, D15, D29 (before the second dose), D57 (before the third dose), D85, and D113.

Out of the 23 participants in the Rimmyrah treatment group, 2 (8.7%) were ADA positive at baseline. In the Lucentis group (n=25) only one participant (4.0%) was ADA positive at baseline. All other participants were ADA negative at baseline.

In general, the incidence of anti-drug antibodies during the study QL1205-001 was low and more or less comparable between both treatment groups. Although, the number of ADA positive participants was slightly higher for Rimmyrah compared to the Lucentis at all time points, except day29, no more than 3 subjects at one time point were ADA positive. The proportion of subject who were ADA positive at any time point ranged between 4.0% and 13.6% during the study.

No data of NAbs are available. According to the applicant, all blood samples from ADA-positive subjects were tested for NAb and were detected as negative.

Table 14. Incidence of Anti-drug Antibodies to Ranibizumab - (SS)

	QL1205 (N = 23)	Lucentis ® (N = 25)
Baseline		
N	23	25
Negative	21 (91.3%)	24 (96.0%)
Positive	2 (8.7%)	1 (4.0%)
D15		
N	23	24
Negative	20 (87.0%)	24 (100.0%)
Positive	3 (13.0%)	0 (0.0%)
D29		
N	23	25
Negative	22 (95.7%)	24 (96.0%)
Positive	1 (4.3%)	1 (4.0%)
D57		
N	23	25
Negative	20 (87.0%)	24 (96.0%)
Positive	3 (13.0%)	1 (4.0%)
D85		
N	22	25
Negative	20 (90.9%)	24 (96.0%)
Positive	2 (9.1%)	1 (4.0%)
D113		
N	22	24
Negative	19 (86.4%)	23 (95.8%)
Positive	3 (13.6%)	1 (4.2%)

a. Data Source: Study QL1205-001 CSR Listing 14.3.11.1
b. Note: Percentages are calculated using the number of non-missing subjects in each group as the denominator.

Secondary pharmacology

VEGF Concentration (Study QL1205-001)

In study QL1205-001 the VEGF concentration before and after administration of ranibizumab has been assessed at different time points (at baseline, 3h, 24h, 96h, day8, day 29 (before the second administration), day 57 (before the third administration) and day 85 after drug administration).

Overall, a decreasing trend was observed in the median plasma VEGF concentration following a single IVT administration of 0.5 mg Rimmyrah or Lucentis, which returned to baseline levels closely before the next dose (day 29). After multiple administration of study drug, e.g. at 85 days after drug administration, the median VEGF concentration was lower in the Lucentis treatment group (14.600 pg/mL) compared to the Rimmyrah treatment group (21.900 pg/mL).

2.4.4. Discussion on clinical pharmacology

Rimmyrah (Ranibizumab), a recombinant humanised Immunoglobulin G (IgG) 1 kappa isotype monoclonal antibody fragment designed for intraocular use, was established to demonstrate the biosimilarity between Rimmyrah and the reference medicinal product Lucentis in the most sensitive indication "neovascular age-related macular degeneration (nAMD). The PK profile, was evaluated within the confirmatory comparative clinical safety and efficacy study QL1205-002 and in the supportive Phase 1 study QL1205-001.

In studies QL1205-001 and QL1205-002, the comparability exercise was performed between EU-Lucentis reference medicinal products and the Rimmyrah intended to be marketed in the EU. This is endorsed.

Usually, a pivotal PK study is recommended to obtain information on biosimilarity. However, in this case, no PK studies in healthy volunteers were conducted for ethical and safety reasons (IVT mode of application) and no pivotal PK study in the target population was performed. This is considered to be acceptable and was endorsed by the EMA through SA (EMA/CHMP/SAWP/780505/2018) because the systemic exposure is expected to be too low for a formal bioequivalence study and it is therefore instead assessed as a safety parameter in a subset of patients within the confirmatory study, which allows further investigation of the clinical impact of variable pharmacokinetics and possible changes in the PK over time. Thus, sampling for Cmax following the first and the 6th dose in the pivotal study is intended to confirm that there is no excess systemic exposure of Rimmyrah compared to the reference medical product. In addition, a supportive Phase 1 clinical study in patients with wAMD (QL1205-001) was also conducted (requested by the Chinese CDE) in which PK characteristics of Rimmyrah being compared to Lucentis was a secondary objective. For the pivotal study (QL1205-002) a comparative pharmacokinetic analysis of the systemic exposure at both start of treatment and steady-state between the reference and the biosimilar product was conducted for the MAA, which was correlated with the product safety profile, in consideration that a formal statistical bioequivalence analysis would not have been meaningful.

Bioanalytical methods

Pharmacokinetic assay

Pharmacokinetic assay (Validation Report: 8402-932; pivotal phase 3 study- QL1205-002)

The PK assay method has been developed and validated to quantitatively detect Rimmyrah and Lucentis concentration in human serum by using electrochemiluminescence assay (ECLA).

The response function and calibration range (calibration curve performance), bioanalytical similarity between Rimmyrah and Lucentis, dilution linearity, no hook effect and stability of the analyte were confirmed. No interference was observed for Rimmyrah up to 3.0 ng/mL and for Lucentis up to 1.0 ng/mL VEGF.

The intra- and inter-assay accuracy and precision runs of the quality control samples for Rimmyrah and Lucentis were within the acceptance criteria for the QC-levels 90 pg/mL (Low), 3,000 pg/mL (Medium), 15,000 pg/mL (High), and 20,000 pg/mL (ULOQ) and are considered acceptable. However, the intra-assay accuracy (-39.5 %) and intra-assay TE (44.2%) for the LLOQ (30 pg/ml) of Lucentis (batch VB01) did not met the acceptance criteria. However, since the inter-assay accuracy for the LLOQ of Lucentis was within the acceptance criteria and all 6 runs were included in the calculation, this is considered acceptable. In addition, one outlier by Rimmyrah (batch VB01) has also been detected for the intra-assay accuracy (-57.6%) and intra-assay TE (59.5%) for the LLOQ (30 pg/ml), but this outlier (batch VB01) was not included in the calculation. Thus, only 5 runs of Rimmyrah at LLOQ (30pg/mL) met the acceptance criteria at initial submission. Since the acceptance criteria for within-run accuracy according to ICH guideline M10 on bioanalytical method should be met in at least 6 runs, an additional accuracy and precision run (VB43R) for Rimmyrah was conducted upon request to verify the method performance. This additional run, met the acceptance criteria, and after the LLOQ outlier batch VB01 was excluded from the calculation, the inter-assay precision at LLOQ of the 6 remaining runs was 12.1% and thus is considered acceptable. Therefore, run VB01 may be an isolated case and the assay performance appears to be acceptable.

The selectivity and matrix effect seem to be acceptable. No effect from lipemia on the quantification of Rimmyrah and Lucentis and no effect from haemolysis on the quantitation of Rimmyrah and Lucentis at haemolysis levels up to 20,000 pg/mL were identified. Upon request, also selectivity data analysed on patient serum for Rimmyrah and Lucentis has been provided. All samples met the acceptance criteria and no matrix effect was identified.

In addition, long-term stability for Rimmyrah/ Lucentis and stock solution stability have been assessed and provided in an addendum report to the Validation report initially submitted (Study 8402-932-ADDENDUM REPORT 23Feb2023). Based on the data provided, the freezer stability up to 35 months for Lucentis/Rimmyrah met the acceptance criteria and indicated that stability was retained at least for 1034 days following storage at -60 to -80°C. In addition, stock stability for Rimmyrah was demonstrated for 199 days at a storage condition of -60 to -80°C.

Based on the data provided, the acceptability of the method performance and the reliability of analytical results appear to be appropriated.

Pharmacokinetic assay (Validation report: Q3206MVHuSe01; phase 1 study- QL1205-001)

The PK assay method has been developed and validated to quantitatively detect Rimmyrah and Lucentis concentration in human serum by using electrochemiluminescence assay (ECLA).

The response function and calibration range (calibration curve performance), intra- and inter-assay accuracy and precision, selectivity, dilution linearity, no hook effect and stability of the analyte were confirmed.

No interference was observed for Rimmyrah up to 3.0 ng/mL and for Lucentis up to 1.0 ng/mL VEGF. However, the specificity in the presence of VEGF has not been demonstrated by accuracy at the LLOQ and ULOQ. Although in general, it is essential to determine the minimum concentration of the related molecule where interference occurs, as the phase 1 study is only supportive for the pivotal phase 3 study no question was raised in this special case.

In addition, although, no effect from hyperlipidemia on the quantification of Rimmyrah and Lucentis and no effect from haemolysis on the quantitation of Rimmyrah and Lucentis at haemolysis levels up to 20,000 pg/mL were identified, it was understood that no selectivity/matrix effect were analysed on patient serum or on individual donors fortified with Rimmyrah and Lucentis. These data are considered relevant for the assay validation. However, as the phase 1 study is only supportive for the pivotal phase 3 study, no question was raised in this particular case.

Overall, the results derived from these validation activities in general support the conclusion that the assay (ECLA method) might be reliable and suitable for measuring Rimmyrah and Lucentis concentration in human serum samples. However, there are still some uncertainties related to the validation described above. Overall, the phase 1 study is only supportive for the pivotal phase 3 study, hence these uncertainties have no substantial consequences on the biosimilarity assessment and on the benefit/risk conclusions.

VEGF assay (Validation Study Number: Q3206MVHupl04; study phase 1 – QL1205-001)

For the ability to exclude an interference with endogenous components, potential interference of VEGF concentrations was evaluated by fortifying and analysing Rimmyrah or Lucentis QC samples at LLOQ and ULOQ concentrations in human plasma with CTAD anticoagulation using the MSD-Based sandwich ECLA platform.

To investigate the accuracy and precision of the method with the buffer QC samples at low (LQC: 2 pg/mL), medium (MQC: 30 pg/mL) and high concentrations (HQC: 525 pg/mL), a total of 6 independent analytical runs were performed. However, no accuracy and precision of the method at the LLOQ (0.684 pg/mL) and ULOQ (700 pg/mL) were performed. The precision of matrix QC samples was investigated only at low and high concentration levels (LMC and HMC). Although the intra- und inter batches met the acceptance criteria specified in the methodological validation protocol [QCs: %CV ≤ 20% (% CV ≤25%

at ULOQ and LLOQ), % RE not to exceed ± 25%; Total error between batches: QCs: ≤30%] this method validation approach is considered to be not fully in accordance with the ICH guideline M10 on bioanalytical method validation. The QCs should be prepared at a minimum of 5 concentration levels including the LLOQ and the ULOQ. Only for non-accuracy and precision validation runs, low, medium and high QCs may be analysed in duplicates. The intra- and inter-precision data were acceptable.

The matrix recovery (selectivity) of healthy individuals and patient individuals with AMD was investigated at two concentration levels: blank matrix (Blank) and low concentration quality control (LQC 2 pg/mL VEGF), which were investigated in 6 individuals, each sample was repeated 3 times. It appears that no significant matrix effect was observed in any of the tested human plasma. However, in accordance with the ICH guideline M10 on bioanalytical method validation, selectivity should be evaluated using blank samples obtained from at least 10 individual sources and by spiking the individual blank matrices at the LLOQ and at the high QC level.

The short-term stability (bench-top) investigated the stability of matrix quality control samples (LMC [3.65 pg/mL], HMC [13 pg/mL]) stored at room temperature for 24 hours or at 2-8°C for 24 hours. The acceptance criteria specified in the methodological validation protocol (at least 2/3 of the validation samples have RE% within ±30% of the baseline concentration; CV% ≤30%) are not in accordance with the ICH guideline M10 on bioanalytical method validation (The mean concentration at each QC level should be within ±20% of the nominal concentration). However, the predefined acceptance criteria specified in the methodological validation protocol were established based on the methodologically data and the commercial kit COA and the mean %CV of all OC samples were within ±20%, this is considered acceptable. The mean %RE of the HMC at ART 24 hours was -10% and at 2°C-8°C -9.2% and the mean %RE of the LMC at ART 24 hours ranged between -34.8% to -21.4% and at 2°C-8°C was -24.7%.

Overall, 10 ng/mL Lucentis and 1 ng/mL Rimmyrah is the highest concentration that not affect the determination of VEGF concentration in biological samples.

In conclusion, based on the data provided, the assay validation approach is not fully in accordance with the ICH guideline M10 on bioanalytical method validation. However, the bioanalytical assay for the VEGF concentration in human plasma is adopted a commercially available kit (V-PLEX Plus Human VEGF Kit, Meso Scale Discovery) based on the MSD platform, which designed specific for the VEGF detection. In addition, since the predefined acceptance criteria specified in the methodological validation protocol were established based on the methodologically data and the commercial kit COA, since the predefined acceptance criteria were met and since these data are only supportive for the pivotal phase 3 study, this can be considered acceptable and no question is raised.

Anti-drug-Antibody assay (pivotal phase 3 study- QL1205-002 and supportive phase 1 study -QL1205-001)

A 3-tiered approach for the determination of anti-drug antibodies (ADA) against QL1205/Lucentis in human serum samples, using a bridging immunoassay based on MSD, compromising a screening, confirmation, and titer/quantitative stratification methods to confirm the existence of anti-Rimmyrah/ Lucentis antibodies. This strategy for immunogenicity assessment is in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and is considered acceptable.

Overall, the assay validation approach developed and validated for the ADA assay clinical sample analysis, is generally considered to be acceptable. The data presented in this validation reports for both studies, phase 3 and phase 1, indicate that the method described appears to be suitable for the detection, confirmation and quantification of Anti-Rimmyrah antibodies in human serum.

However, although one issue regarding the assay validation for study phase 1 remains (no selectivity was confirmed in haemolytic or lipemic samples), as the phase 1 study is only supportive for the pivotal phase 3 study, no question was raised.

Neutralizing antibody assay (pivotal phase 3 and supportive phase 1 study)

A competitive ligand binding assay (CLBA) has been developed and validated based on MSD Platform for determination of neutralising antibodies (NAb) against Rimmyrah and Lucentis monoclonal antibodies in human serum samples. As QL1205/Lucentis is an antagonistic mAbs, the ligand binding assays may be appropriate. Due to the mode of action of ranibizumab, the inhibition of binding activity which is measurable by the assay in case that nAbs are present reflects the neutralizing capacity. Therefore, the assay format is considered to be adequate.

Overall, for both studies, the data provided in the validation reports indicate that the method appears to be suitable for the qualitative and quasi-quantitative measurement of anti-Rimmyrah and anti-Lucentis neutralization antibodies (Nab) in human serum.

Absorption, distribution, metabolism, elimination (ADME)

No new data regarding absorption, distribution, metabolism and elimination of Rimmyrah were collected from the study Phase 1 (QL1205-001) and Phase 3 (QL1205-002). This is in general considered acceptable because the biosimilar candidate relies on the information already known about the reference product.

Special populations

No new data were collected on pharmacokinetics in special populations from the biosimilar study QL1205-001 and QL1205-002. This is in general considered acceptable because the biosimilar candidate relies on the information already known about the reference product.

Thus, no formal studies have been conducted to examine the pharmacokinetics of Rimmyrah in patients with renal/hepatic impairment. 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.

Overall, the QL-1205 SmPC regarding pharmacokinetics in special populations is in line with EU-Lucentis SmPC, which is considered appropriate.

Clinical studies QL1205-002 and QL1205-001

Pharmacokinetic profile of study QL1205-002

Study QL1205-002 was a randomised, double-masked, parallel-group, global multicenter Phase 3 in subjects with wAMD to demonstrate therapeutic equivalence of Rimmyrah compared to EU Lucentis. A total of 616 wAMD patients were randomised in a 1:1 ratio to receive either Rimmyrah (0.5 mg (0.05 mL), n=308) or Lucentis (0.5 mg (0.05 mL), n=308). Administration of the products was via intravitreal injection once every four weeks, 13 consecutive dosing until Week 48. In this study PK and Immunogenicity were assessed as secondary endpoints. The PK endpoint is the maximum observed

concentration at certain time points. Immunogenicity (anti-ranibizumab antibodies, antidrug antibody [ADA], and neutralizing ADA [NAb]) measurements are performed before treatment at Day 1, Week 4, Week 8, Week 12, Week 24, and Week 52. PK analysis was performed in a subset of 73 subjects, including 33 subjects for Rimmyrah and 40 subjects for Lucentis. The demographic and baseline characteristics for the PK Set appear to be more or less similar between Rimmyrah and Lucentis. No clinically relevant difference was observed.

For the evaluation of the PK profile, serum concentration was evaluated at specific time points (at baseline [Day 1], on Day 2, and at steady-state at Week 20) in a subset of 73 subjects (33 subjects for Rimmyrah and 40 subjects for Lucentis) of the clinical QL1205-002 study to detect any notable differences in systemic exposure between the Rimmyrah and EU Lucentis in wAMD patient population. The chosen time points for measuring the PK profile were agreed in the EMA Scientific advice. In addition, it was agreed by the CHMP in the follow-up advice (EMA/CHMP/SAWP/780505/2018 Scientific Advice) that the comparative clinical PK is to be performed in a subset (10% of total patients) of approximately 60 AMD patients (30 patients in each arm) in the confirmatory comparative efficacy trial. It was also agreed that the comparison of PK could be performed in a statistical non-confirmatory manner but should still be comparative in nature. In addition, a presentation of 95% confidence intervals was agreed, too, by the CHMP. Thus, the chosen time points for measuring the PK profile and the selected PK sample size of 73 subjects [33 subjects for Rimmyrah, 40 subjects for Lucentis] is considered to be sufficient to characterise the PK profile in this case, or at least to demonstrate no significant differences in the serum concentration between the biosimilar and the originator.

Not all samples of the Pharmacokinetics Set have been analysed, neither for Rimmyrah nor for Lucentis. Of the 33 patients, which received Rimmyrah treatment, 32 PK samples from Baseline (Day1), 31 samples of Day 2 and 28 samples of week 20 were analysed. In comparison, of the 40 patients, which received Lucentis 37 PK samples from Baseline (Day1), 38 samples of Day 2 and 32 samples of week 20 were analysed. Upon request, information on missing PK samples from the PK analysis at each time point and for each subject was provided. Based on this subsequently submitted data, a total of 19 missing PK samples from the PK analysis set have been reported. However, it is considered unfortunate that in the already quite small PK population, a complete set of samples is not available for all patients. Nevertheless, since approx. 30 patients per treatment group appear to provide a complete PK sampling dataset, and 30 patients per group was considered sufficient for the PK analysis by the CHMP, this is considered acceptable.

Based on the data provided, a serum concentration of Lucentis and Rimmyrah was already observed at baseline (Day1). The geometrical mean was 409.697 pg/mL for Rimmyrah and 389.504 pg/mL for Lucentis. The pre-dose levels might have affected the efficacy and safety results, including immunogenicity, and might have been a result of faulty bioanalysis method. Upon request, the data of 10 treatment-naïve patients with quantifiable concentrations of either Rimmyrah or Lucentis at baseline (pre-dosing) was provided. Based on the information available, no error occurred for the sample receipt and sample analysis process. Although, the selectivity testing in the assay fulfilled the acceptance criteria and thus the assay appears to be adequate and although according to the applicant, no evidence pointing to previous anti-VEGF treatment and no misconduct of the site staff or protocol deviations were identified, the detected serum concentrations at baseline (pre-dosing) of Lucentis and Rimmyrah are still questionable, especially for those patients with higher serum concentrations. However, the provided post-hoc sensitivity analysis of the primary efficacy endpoint, which excluded these 10 subjects with detectable serum concentration at baseline, demonstrated that these 10 subjects did not have a major impact on the results and that Rimmyrah and Lucentis can be considered biosimilar based on the available data.The serum concentration of Rimmyrah and Lucentis measured at Day1, Day2 and week 20 were similar in both treatment groups for all measurement time points. The geometrical mean concentration for post-dose time points was 1907.958 pg/mL for Rimmyrah and 1910.067 pg/mL for

Lucentis at day 2 and 1435.013 pg/mL for Rimmyrah and 1741.314 pg/mL for Lucentis at week 20. The observed variability (CV%) was very high and ranged between 105.1% and 112.8% for Rimmyrah and between 106.5% and 121.0% for Lucentis® for post-dose time points and error bars for both treatments overlapped. In general, very high standard deviation was observed in both treatment groups, Rimmyrah and Lucentis, at all measurement time points. The post-dose GeoRatio (CI 95%) for the serum concentration of QL1205/Lucentis was 82.4% (CI95%: 43.6-155.9) at day 2 and 99.9% (64.5-154.8) at Week 20. Since the point estimate was quite well obtained, it can be assumed that the systemic availability of the two products is more or less comparable.

As described in the Lucentis SmPC, upon monthly intravitreal administration of Lucentis 0.5 mg/eye, serum ranibizumab Cmax, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/ml, and Cmin is predicted to generally range between 0.07 and 0.49 ng/ml based on population PK model.

The range of the maximum observed concentration of both treatments are far above these predicted Cmax values [QL1205: 15574.87 pg/mL, Lucentis: 19464.09 pg/mL]. Thus, the maximum concentrations of both the treatment [QL1205: 15574.87 pg/mL, Lucentis: 19464.09 pg/mL] 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]. Moreover, also the maximum observed concentration of Rimmyrah and Lucentis before treatment in this study was 16975.34 pg/mL and 15187.38 pg/mL respectively. Although, the mean and median of concentrations were within the predicted range of Lucentis Cmax, the observed maximum concentration values for individual subjects 1 day after dosing were within the active range of ranibizumab and quite above the general predicted Lucentis Cmax range for both products. Based on subsequently submitted data, only two patients, one in the Lucentis group and one in the Rimmyrah group, showed very high concentration (>10 ng/mL) of Lucentis/Rimmyrah during the study. However, the occurrence of very high concentration (>10 ng/mL) was balanced between both treatment groups, and detected from baseline on (pre-dosing). In addition, no adverse events that occurred in patients with high plasma concentrations were considered related to the study treatment or procedures and were not reported more than once. Therefore, it is considered unlikely that these high concentrations are related to study treatment. In addition, the assay used in this study appears to be appropriated, and might be more sensitive than the assay used in the originator study. However, it could also be that these two patients may not have been treatment-naïve at study entry, as was actually required for study eligibility.

Pharmacokinetic profile of study QL1205-001

Study QL1205-001 was a randomised, double-blinded, parallel-group, active-controlled Phase 1 study to compare the safety, PK, and PD of Rimmyrah and Lucentis (China) in patients with neovascular (wet) age-related macular degeneration (wAMD). 48 subjects with wAMD were randomised in a nearly 1:1 ratio to receive either Rimmyrah (n=23) or Lucentis (n=25). In this study pharmacokinetic characteristics of Rimmyrah or Lucentis in patients with wet-AMD after intravitreal injection was assessed as secondary objective. There were 12 blood sample collection points in total to detect the drug concentration of ranibizumab.

The demographical characteristics were comparable between both treatment groups for ethnicity (100% Han Chinese), gender (QL1205:73% male/26.1% female vs Lucentis: 72% male/28.0% female),median height (QL1205: 165cm vs Lucentis: 166 cm) and weight (QL1205: 63 kg vs Lucentis: 65 kg). The median age was slightly higher in the Rimmyrah treatment group (68 years) compared with the originator treatment group (63 years).

In contrast the baseline characteristics of prior/Concomitant medical history showed some differences between the treatment groups. Although, most of the participants in study QL1205-001 had prior/concomitant medical history (ocular and systemic diseases other than AMD), the number of patients with prior/concomitant medical history (ocular and systemic diseases other than AMD) was higher in the Rimmyrah treatment group (91.3%) than in the Lucentis treatment group (84.0%). In addition, the number of participants with other AMD-related medical history was higher in the Rimmyrah group (26.1%) than in the Lucentis group (12.0%). In contrast, the number of participants with wAMD in the fellow eye (QL1205: 8.7% vs Lucentis: 16%) and with AMD prior treatment history (QL1205: 8.0% vs Lucentis: 26.1%) was higher in the Lucentis treatment group than in the Rimmyrah treatment group.

Based on the "Mean Serum Drug Concentration vs Time Curve" the serum concentration of Rimmyrah and Lucentis seems to be similar at all measured time points ((D1: before and 3h after administration), 24h (D2), 48h, 96h, 168h, 336h, 504h, D29) and the mean value of Cmax was similar between both treatment groups (QL1205= 4538 pg/ml vs. Lucentis=4472.82 pg/ml). The geometrical mean was a bit lower in the Rimmyrah group compared to the Lucentis group (QL1205= 2586.73 pg/mL vs. Lucentis= 3102.94 pg/mL)

The mean of AUC0-t and AUC0-inf were slightly higher in the Rimmyrah treatment group (AUC0-t: 556810.43 h*pg/ml, AUC0-inf: 695257.02 h*pg/ml) compared to the Lucentis treatment group (AUC0-t: 507521.40 h*pg/ml, AUC0-inf: 594139.05 h*pg/ml). However, based on the provided data no clinical significant differences between Rimmyrah and Lucentis were observed. In addition, a high variability (CV%) for Cmax was observed in both groups (QL1205: 167.46%; Lucentis:114.22%).

As described in the Lucentis SmPC, upon monthly intravitreal administration of Lucentis 0.5 mg/eye, serum ranibizumab Cmax, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/ml, and Cmin is predicted to generally range between 0.07 and 0.49 ng/ml.

The range of the observed maximum concentration of both treatments are far above [Cmax: QL1205: 35400.00 pg/mL, Lucentis: 23800.00 pg/mL; Cmin: QL1205: 706.00 pg/mL, Lucentis: 918.00 pg/mL] these Cmax and Cmin values described in the SmPC of Lucentis. 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]. Although, the mean and median of Cmax were within the predicted range of Lucentis Cmax, the maximum values of Cmax were within the active range of ranibizumab and quite above the general predicted Lucentis Cmax range. However, no major safety concerns have been identified. The severity of the drug-related adverse events were mild or moderate in subject that had serum concentration (Cmax) exceeding 2.90 ng/mL, no adverse event was reported more than once and the number of reported adverse reaction in patients with Cmax exceeding 2.90 ng/mL was low. Thus, the observed high serum concentration did not raise any major safety concerns compared to the lower serum concentration, based on the information provided. In addition, the assay used in this study might be more sensitive than the assay used in the originator study, as it determines the concentration of all ranibizumab entering the system circulation stream (free ranibizumab and the ranibizumab-VEGF complex), which could explain the detection of higher serum concentrations.

Overall, the Phase 1 QL1205-001 study is considered to be supportive for the pivotal Phase 3 clinical study QL1205-002. However, the results of the clinical phase 1 study are not presented in the same way as those of the phase 3 study and differences in the study population and study design exist between both studies, so that a direct comparison of the results cannot be made. In general, comparison between studies should be considered with caution. Based on the provided serum concentration vs. time curves, the mean of the serum concentration observed in the Phase 3 study appears to be lower compared to the Phase 1 study. These differences could be due to different patient populations in the studies. In both studies the observed variability (CV%) and standard variation was high, which may be caused by the

administration of IVT injection. Although, the number of patients enrolled in the pharmacokinetics analysis set is limited in both studies (Study QL1205-001: n=48; Study QL1205-002: n=76), both studies demonstrated similar PK data between the biosimilar and the originator.

Anti-drug antibodies (ADA)

Anti-drug antibodies (ADA) – Study QL1205-002

Rimmyrah, as a therapeutic protein drug, has the potential to induce immunogenicity. Therefore, the immunogenicity profile was evaluated in the phase 3 study as one of the secondary endpoints regarding the incidence of ADA and NAbs. The clinical immunogenicity database for Rimmyrah comprises results of the Clinical Phase 3 Study QL1205-002, which was designed to demonstrate therapeutic equivalence between Rimmyrah and Lucentis. A 3-tiered approach for the determination of anti-drug antibodies (ADA) against QL1205/Lucentis in human serum samples, using an Immunodepletion-bridging Electrochemiluminescence Assay (IMD-B ECLIA) based on MSD, compromising a screening, confirmation, and titer/quantitative stratification methods to confirm the existence of anti-Rimmyrah/ Lucentis antibodies.

Blood samples for determination of immunogenicity were collected at 6-time points during the test period, before dose administration on Day 1 (Baseline), Week 4, 8, 12, 24 and 52.

In general, a similar number of ADA positive patients was observed at baseline (Day1) and at the post-treatment time points (week 4, 8, 12, 24 and week 52). Based on the safety set, 294 patients out of 309 patients in the Rimmyrah treatment group, provided blood samples for the pre-treatment ADA assessment. 12 (4.1%) of these 294 patients were ADA positive at pre-treatment (day 1). No information has been provided about the blood samples of the 15 participants that were not included in the ADA assessment. In the Lucentis treatment group, 295 patients out of 307 patients provided blood samples for the pre-treatment ADA assessment. 11 (3.7%) of these 295 patients were ADA positive at pre-treatment (day 1). No information has been provided about the blood samples of the 12 participants that were not included in the ADA assessment. Nevertheless, in total 27 patients out of 309 patients in the Rimmyrah treatment group (8.7%) and 28 patients out of 307 patients in the Lucentis group (9.1%) were detected ADA positive during the study up to week 52. Thereof, two patient in the Rimmyrah group (2/27 [7.4%]) and three patients in the Lucentis group (3/28 [10.7%)] had neutralizing antibodies during the study up to week 52.

A slight increase of ADA positivity was observed from baseline to week 24 in both treatment groups. In the post-treatment detection of ADAs until week24, ADAs were detected in 12-15 participants (4.4%-5.6%) in the Rimmyrah treatment group and in 15-18 participants (5.4%-6.8%) in the Lucentis group. However, the detected proportion of subjects who were ADA positive at any time point was low (approximately 4% to 7%) until week 52 and were similar between both treatment groups (QL1205: 4.1%-5.6%; Lucentis 3.7%-6.8%). In addition, the number of treatment-induced ADAs was even lower (approximately 1% to 5%) during the study up to week 52 and also the number of neutralizing antibodies at any time point was very low and similar between both treatment groups. Thus, no clinical significant differences between both groups were identified and the immunogenicity is expected to be low.

Although, the incidence of anti-drug antibodies and the frequency of NAb during the study QL1205-002 was low the impact of ADA status on PK, efficacy and safety was requested. Based on the subsequently submitted information, no specific trend of a relationship between the ADA status and the serum concentration could be identified. However, the data need to be interpreted with caution, since the number of ADA positive patients was very small in the PK data set (QL1205: n=4-5; Lucentis: n=2-3), and usually more data would be required for a final conclusion. In addition, the occurance of ADA positive samples in the overall safety set was similar between both treatment groups during the study up to week

52 (QL1205: n=27/309 [8.7%] vs. Lucentis: n=28/307 [9.1%]). Although a slightly potential difference in the number of patients with at least one TEAE between the originator and biosimilar in ADA positive patients has been observed (QL1205: n=22 [81.5%] vs. Lucentis: n=20 [71.4%]), the numerical difference in ADA positive patients between both groups was small and, no new safety signal or major safety concern have been identified in ADA positive patients compared to ADA negative patients. Moreover, since no TEAE (drug hypersensitivity, anaphylaxis or intra-ocular inflammation) were reported for ADA positive patients, the safety risk due to clinically relevant treatment-emergent ADAs is assumed to be low. Overall, it is considered unlikely that the ADA statut on PK and on safety will have a negative impact on the biosimilarity.

In contrast, it appears that ADA positive patients in the Rimmyrah treatment group might have a loss of efficacy, so that a potential difference between the originator and biosimilar in ADA positive patients on the efficacy endpoint BCVA at Week 8 cannot be fully excluded so far. Nevertheless, it needs to be considered, that the total number of ADA positive patients was quite small in general. In addition, the number of treatment-induced ADAs was even smaller and more or less similar between both treatment groups. Thus, more data would be required to clarify whether the observed differences between both treatment groups in ADA positive patients are a chance finding or not. Therefore, the results should be interpreted with caution. However, among the ADA-positive subjects, the frequency of NAb was quite low (≤2 subjects at any time point). Overall, two patient in the Rimmyrah group (2/27 [7.4%]) and three patients in the Lucentis group (3/28 [10.7%)] had neutralizing antibodies during the study up to week 52. Therefore, based on the provided data, since only one subjects in the Rimmyrah group had a positive NAb result between day 1 and week 8, no treatment failure due to loss of therapeutical function of QL-1205 would actually be expected. Overall, more data would be needed for a meaningful conclusion on whether the ADA status affects PK, safety and efficacy.

Anti-drug antibodies (ADA) – Study QL1205-001

In the clinical Phase 1 study QL1205-001, 48 wAMD subjects in total were enrolled and randomised, of which 23 subjects received Rimmyrah and 25 subjects Lucentis. Blood samples for determination of immunogenicity were collected at 0h (before the first dose), D1, D15, D29 (before the second dose), D57 (before the third dose), D85, and D113. The clinical immunogenicity database for Rimmyrah comprises results of the Clinical Phase 1 Study QL1205-001, which was designed to demonstrate therapeutic equivalence between Rimmyrah and Lucentis. Immunogenicity was one of the secondary endpoints regarding the incidence of ADA and NAbs.

This study ADAs were measured using the validated MSD platform bridging ligand-binding electrochemiluminescent (ECL) method and NAbs were measured using the competitive ligand binding (CLB) assay.

Blood samples of almost all participants at the different time points and from the different treatment groups (QL1205/Lucentis) were assessed for anti-drug antibodies.

Out of the 23 participants in the Rimmyrah treatment group, 2 (8.7%) were ADA positive at baseline. In the Lucentis group (n=25) only one participant (4.0%) was ADA positive at baseline. All other participants were ADA negative at baseline. This is considered acceptable.

In general, the incidence of anti-drug antibodies during the study QL1205-001 was low. Although, the number of ADA positive participants was higher for Rimmyrah compared to the Lucentis at all time points, except day29, no more than 3 subjects at one time point were ADA positive. The proportion of subject who were ADA positive at any time point ranged between 4.0% and 13.6% during the study. However, as the proportion of ADA was higher in the QL1205-001 group in comparison to Lucentis group, a subgroup analysis of efficacy and safety according to the baseline ADA positive/negative status has been

provided upon request. Based on the limited data available, no conclusion can be drawn on the impact of ADAs on the safety and on BCVA.

No data of NAbs are available. According to the applicant, all blood samples from ADA-positive subjects were tested for NAb and were detected as negative.

Although, the incidence of anti-drug antibodies during the study QL1205-001 was low, the impact of ADA status on PK and the ADA titers for the ADA positive participants were requested. Only one subject in the Lucentis group and three subjects in der Rimmyrah treatment group were tested positive for ADAs. Almost all patients with positive ADAs had an ADA titer lower 20 and no-drug-related AEs have been reported. Overall, based on the limited data available, no conclusion can be drawn on the impact of ADAs on PK. However, no clear influence of the ADA status and titre on the safety and on BCVA was observed and no significant differences between Lucentis and Rimmyrah was identified.

Overall, based on the limited data available, the immunogenic potential of ranibizumab (QL1205/Lucentis) appears to be low and support the findings in the Phase 3 study QL1205-002.

VEGF Concentration (Study QL1205-001)

Secondary pharmacodynamics studies were not performed for QL1205. This is in line with the EMA guideline "Guideline on similar biological medicinal products containing monoclonal antibodies: nonclinical and clinical issues" (EMA/CHMP/BMWP/403543/2010).

However, in study QL1205-001 the VEGF concentration before and after administration of ranibizumab has been assessed at different time points (at baseline, 3h, 24h, 96h, day8, day 29 (before the second administration), day 57 (before the third administration) and day 85 after drug administration).

A decreasing trend was observed in the median plasma VEGF concentration following a single IVT administration of 0.5 mg Rimmyrah or Lucentis, which returned to baseline levels closely before the next dose. However, after multiple administration of study drug the biosimilarity between Lucentis and Rimmyrah was questionable, as the median VEGF concentration was lower in the Lucentis treatment group (14.600 pg/mL) 85 days after drug administration compared to the Rimmyrah treatment group (21.900 pg/mL). Although, a decreasing trend was observed in the Rimmyrah and Lucentis groups after a single IVT administration, the median plasma VEGF concentration was similar between Rimmyrah and Lucentis in general and based on the subsequently submitted information, no clear evidence of correlation between activity/systemic suppression range of VEGF and maximum serum concentration values or adverse effects have been observed.

2.4.5. Conclusions on clinical pharmacology

From a PK perspective, no major objections have been identified and the data provided support biosimilarity between Rimmyrah and the EU reference product Lucentis.

From a PD perspective, the mechanism of action of ranibizumab is sufficiently described by the applicant and no concerns are raised given the absence of obvious PD biomarkers in the clinical phase 3 study. However, the PD similarity of Rimmyrah and Lucentis in terms of VEGF inhibition was investigated as part of the supportive phase 1 study (QL1205-001) and no clear evidence of correlation between activity/systemic suppression range of VEGF and maximum serum concentration values or adverse effects have been observed.

2.4.6. Clinical efficacy

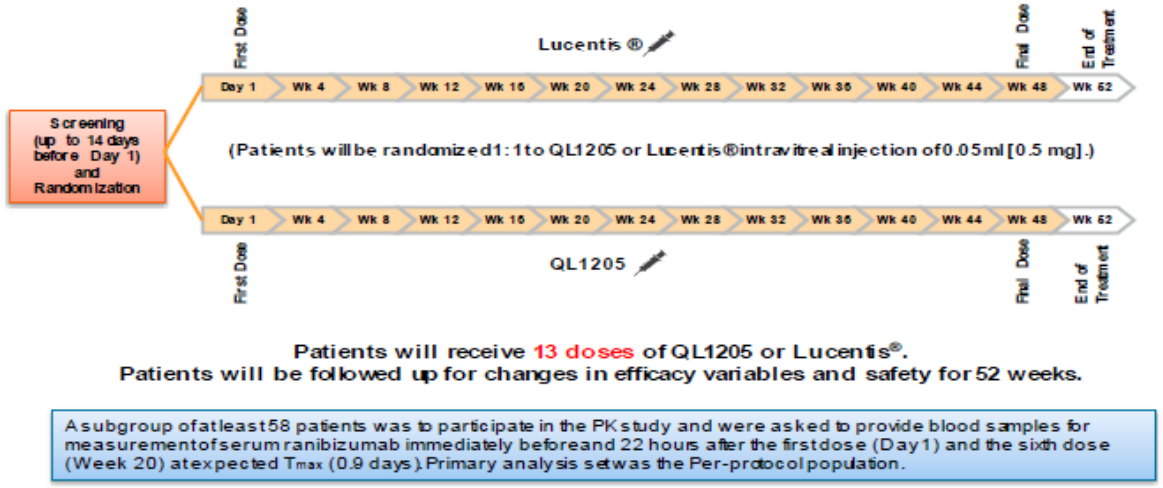
2.4.6.1. Main study

Pivotal Phase 3 study QL1205-002

The study with the title "A Randomized, Phase 3, Double-masked, Parallel-group, Multicenter Study to Compare Efficacy and Safety of Rimmyrah Versus Lucentis in Subjects With Neovascular Age-related Macular Degeneration" was a Phase 3, multiregional, multicentre, double-masked (double-blinded), randomised, parallel-group study in subjects with nAMD.

All subjects were enrolled and randomised in a 1:1 ratio to receive either the reference product EU-Lucentis (0.05 mL of 10 mg/mL ranibizumab) or the investigational product Rimmyrah (0.05 mL of 10 mg/mL ranibizumab) in the study eye once every 4 weeks for 48 weeks.

Figure 2. Study Design



Abbreviations: PK, pharmacokinetics; T_{max}, time to maximum concentration; Wk, Week.

[Figure 2: Figure 1 from Interim CSR]

Subjects were randomised by interactive web response system (IWRS) to receive 13 doses of either Rimmyrah or EU-Lucentis in the study eye. The randomisation scheme included the following stratification parameters to ensure balanced distribution of assignment to the 2 treatments: geographical region where enrolled (2 regions [China/India and Europe]) and the BCVA letters at Baseline (subjects with 66 letters and subjects with >66 letters at Baseline). Subjects were followed for changes in efficacy variables and safety over 52 weeks. Each subject's involvement lasted up to approximately 52 weeks (i.e. 12 months).

The study eye was defined as the eye meeting all of the inclusion criteria and none of the exclusion criteria (i.e. the enrolment criteria). If both eyes met the enrolment criteria, the eye with the worst BCVA assessed at Screening and confirmed at the Baseline (Day 1) visit was selected for treatment. If

BCVA values were identical for both eyes, then the subject may have chosen to select his/her non-dominant eye for treatment or the right eye was selected as the study eye.

The assigned study treatment (Rimmyrah or Lucentis) was administered as an ophthalmic intravitreal injection (IVT). Designated unmasked study staff prepared and administered the study drug and ensured that the masking of the subject was maintained during the injection procedure.

A core efficacy analysis was performed on unmasked study data. After all subjects were randomised and all randomised subjects had 24 weeks data available, an unmasked analysis of primary efficacy and secondary endpoints was performed. The aim of this analysis was to obtain results on the primary endpoint before completion of full follow-up for all subjects. This analysis was not to affect the further conduct of the study.

The study was adequately designed with QL205 versus EU-Lucentis administered into the study eye ITV route for 13 doses every 4 weeks (up to Week 48).

Study duration was 52 weeks, which is considered adequately long to investigate long-term efficacy as well as immunogenicity and safety events.

The treatment scheme and posology are identical to that of EU-Lucentis. The dose of Rimmyrah was selected to reflect the standard clinical use of Lucentis (0.5 mg via ITV route every 4 weeks) to treat nAMD.

A parallel-group design was chosen. This is supported, due to the long average vitreous half-life of ranibizumab of approximately 9 days, and the potential of ADA response.

The selected patient population (neovascular AMD) is considered an appropriate population for a clinical Phase 3 study to demonstrate the similarity in clinical efficacy between Rimmyrah and EU-Lucentis. In the pivotal studies for the treatment of neovascular AMD with Lucentis, the overall difference in BCVA between Lucentis and control group was largest in subjects with AMD, which supports the choice of neovascular AMD as the most sensitive indication compared to DME, RVO, and CNV to detect possibly existing differences between the treatments.

As agreed during the SA procedure, 24 weeks data were provided with the initial MAA submission, and the full 12 months data have been submitted during the procedure with the 120-day response package.

Methods

Study Participants

A total of 616 subjects with nAMD were randomised in a 1:1 ratio to receive either Rimmyrah (0.5 mg/0.05 mL, n=308) or EU-Lucentis (0.5 mg/0.05 mL, n=308).

Inclusion criteria

1. Willingness and ability to undertake all scheduled visits and assessments as judged by the investigator.

2. Aged ≥50 years at Screening.

3. Males, or females of non-childbearing potential (eg, permanently sterilized or postmenopausal [defined as 12 months with no menses without an alternative medical cause before Screening]).

4. Newly diagnosed, treatment-naive, active subfoveal CNV lesion secondary to AMD in the study eye. Active CNV meant presence of leakage was evidenced by FA and intra- or sub-retinal fluid as evidenced by OCT that was confirmed by the central reading center during Screening (before randomization).

5. Total lesion area ≤9.0 disc area (DA) in size (including blood, scars, and neovascularization) as assessed by FA in the study eye and confirmed by the central reading center before randomization.

6. The area of CNV was to be ≥50% of the total lesion area in the study eye confirmed by the central reading center before randomization.

7. Best corrected visual acuity of 20/40 to 20/200 in the study eye using ETDRS chart (≤73 and ≥34 ETDRS letters) at Screening and Day 1 before randomization.

8. Fellow eye is not expected to need any anti-VEGF treatment for the duration of study participation.

9. Written ICF obtained before any study-related procedures were performed.

10. Male subjects of reproductive potential must be willing to completely abstain from sexual intercourse or agree to use an appropriate method of contraception from the time of signing the ICF and for the duration of study participation through 3 months after the last dose of study drug. The investigator and each subject are to determine the appropriate method of contraception for the subject during the participation in the study.

a. A male of reproductive potential is any man who has not been surgically sterilized (eg, has not undergone bilateral orchiectomy or vasectomy).

Exclusion criteria

1. Previous ocular treatment/surgery for nAMD in either eye.

2. Previous IVT treatment/vitreal surgery in either eye.

3. Any previous IVT anti-VEGF treatment (eg, bevacizumab, aflibercept, ranibizumab) in either eye.

4. Any previous systemic anti-VEGF treatment.

5. Sub- or intraretinal hemorrhage involving the fovea in the study eye of 50% or more of the total lesion area assessed by FA and confirmed by the central reading center (before randomization).

6. Subfoveal fibrosis or atrophy in the study eye assessed by FA and confirmed by the central reading center (before randomization).

7. Scarring exceeding 50% of total lesion size in the study eye and confirmed by the central reading center (before randomization).

8. Choroidal neovascularization in either eye due to non-AMD causes assessed by FA and confirmed by the central reading center (before randomization).

9. Retinal pigment epithelial tear involving the macula in the study eye as assessed by FA and confirmed by the central reading center (before randomization).

10. Any concurrent intraocular condition in the study eye (eg, cataract or diabetic retinopathy) that, in the opinion of the investigator, could require treatment during the study period to prevent or treat loss of visual acuity.

11. Other intraocular surgery (including cataract surgery) or periocular surgery in the study eye within 3 months before randomization, except for eyelid surgery within 30 days before randomization.

12. Corneal transplant in the study eye.

13. Active or recent (within 28 days before randomization) intraocular, extraocular, and periocular inflammation or infection in either eye, including conjunctivitis, keratitis, scleritis, or endophthalmitis.

14. Current vitreous hemorrhage in the study eye.

15. History of retinal detachment in the study eye.

16. History of macular hole in the study eye.

17. History of idiopathic or autoimmune-associated uveitis in either eye.

18. Aphakia or absence of the posterior capsule in the study eye, unless it occurred as a result of a Yttrium Aluminium Garnet posterior capsulotomy in association with prior posterior chamber intraocular lens implantation.

19. Presence of advanced glaucoma or optic neuropathy that involved or threatened the central visual field in the study eye.

20. History of glaucoma filtering surgery in the study eye.

21. Uncontrolled ocular hypertension in the study eye, defined as IOP ≥25 mmHg despite treatment with anti-glaucoma medication.

22. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia.

23. Contraindication for Lucentis (hypersensitivity to ranibizumab or to any of the excipients, active or suspected ocular or periocular infection, or active severe intraocular inflammation), or known allergic reactions to any ingredients of QL1205.

24. Current treatment for active systemic infection.

25. Subjects with known history of seropositivity for hepatitis B, hepatitis C antibody, HIV antibody, syphilis tests, or any immunodeficiency and/or immunosuppressive disease or active systemic infection. Seropositivity for hepatitis B is defined as (1) positive for hepatitis B surface antigen and (2) positive for hepatitis B virus DNA.

26. Reasonable suspicion of a disease or condition that may render the subject at high risk of treatment complications or affect interpretation of the study results (as judged by the investigator), such as uncontrolled hypertension (systolic blood pressure [BP] >160 mmHg or diastolic BP >100 mmHg), stroke, or myocardial infarction within 6 months before randomization.

27. Participation in another clinical trial within the previous 3 months or any previous participation in a clinical trial of anti-angiogenic drugs with receipt of previous study drug within 3 months of signing the ICF for this study.

28. Topical ocular corticosteroids administered for ≥30 consecutive days in the study eye within 90 days before randomization.

29. Any systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD within 30 days before randomization, and such treatment or therapy is not allowed during the study period. However, dietary supplements, vitamins, or minerals are allowed.

30. PK subgroup only: Contraindication for additional blood sampling (as judged by the investigator).

Removal of Subjects From Therapy or Assessment

Subjects may stop study treatment for any of the following reasons:

• Subject request (ie, withdrawal of consent)

• Use of non-permitted concurrent therapy

• Noncompliance with the study drug or study schedule

• Lost to follow-up (defined as at least 2 missed study visits without any medical reason and without any contact with the study subject, despite the documented investigator's efforts)

• Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator' s opinion, or unacceptable to the subject to continue

• Need for rescue medication

• Investigator request

• Intercurrent illness

• Sponsor request

• Pregnancy

• Treatment failure, as assessed by the treating investigator

• Need for unmasking

Subjects were free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal was documented in the electronic case report form (eCRF).

Subjects withdrawing from the study were encouraged to complete the same final evaluations (ie, End-of-Treatment [EOT]/Week 52/early termination) as subjects completing the study according to the protocol, particularly safety evaluations. The aim was to record data for subjects who withdraw from the study in the same way as for subjects who complete the study.

The selected study population of newly diagnosed nAMD patients with active subfoveal CNV lesion is considered an adequate sensitive and representative study population for the purpose of establishing clinical biosimilarity between Rimmyrah and the originator Lucentis.

The inclusion and exclusion criteria are overall in line with those in the clinical trials performed with Lucentis [Lucentis SmPC] and are considered adequate.

With regard to BCVA boundaries, a lower limit of 20/100 was recommended by CHMP during SA procedure, to obtain a more homogenous group allowing for evaluation of potential further more pronounced loss of vision. In addition, low visual acuity is associated with a higher variability in terms of the number of letters read at the ETDRS chard, reducing the sensitivity of the study. This was not followed by the applicant. Against this background, the applicant was requested to provide a subgroup analysis for the primary EP for the subgroup of patients with a baseline BCVA between 20/40 and 20/100. The applicant has provided the requested analyses in this subgroup.

The mean change in BCVA (letters) at Wk 8 in the subgroup of patients with a BL BCVA between 20/40 and 20/100 was 5.84 (95% CI: 4.51, 7.18) in the Rimmyrah arm and 6.23 in the Lucentis arm (95% CI: 4.80, 7.66) (ITT population). Biosimilary could be concluded, since the 95% CI of the adjusted treatment difference of -0.39 letters was [-2.15; 1.37], which was completed contained in the pre-specified margin of ±3.49 letters. In the PP population, the mean change in BCVA (letters) at Wk 8 in this subgroup was 6.08 (95% CI: 4.69, 7.48) in the biosimilar arm and 6.14 (95% CI: 4.65, 7.63) in the originator arm, with an adjusted treatment difference of -0.06 letters [95% CI: -1.89; 1.78].

The same picture was observed in this subgroup when analysed by region, with similar mean changes in BCVA (letters) for Rimmyrah compared to Lucentis (region Europe: 5.94 vs 6.44 letters BCVA change).

With regard to the size of total lesion area, the applicant followed the CHMP recommendations during SA procedure: a total lesion area ≤ 9.0 disc areas (DA) in size area was implemented as inclusion criterion.

Treatments

The Investigational Medicinal Products (IMPs) were **Rimmyrah** (Rimmyrah) and **EU-Lucentis**.

Subjects were randomized 1:1 to receive Rimmyrah or EU-Lucentis. Both products were administered as an IVT injection of 0.05 mL (0.5 mg).

Table 15. Details of Study Treatments

	Preparations to Be Administered	
	QL1205	**Lucentis**
Manufacturer	Qilu Pharmaceutical Co., Ltd	Genentech/Novartis
Active ingredient	Recombinant anti-vascular endothelial growth factor antigen-binding fragment (ranibizumab biosimilar)	Ranibizumab
Dosage	0.5 mg (0.05 mL of 10 mg/mL active ingredient)	0.5 mg (0.05 mL of 10 mg/mL active ingredient)
Route	Intravitreal injection	Intravitreal injection
Formulation	Excipients (same as in Lucentis): α,α-trehalose dihydrate, histidine, histidine hydrochloride monohydrate, polysorbate 20	α,α-trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections
[redacted]		

[Table 15: Table 2 from Interim CSR]

Selection of doses in the study

The dose and route of administration for Rimmyrah was identical to that of Lucentis. The recommended dose for Lucentis is 0.5 mg (0.05 mL of 10 mg/mL solution) given as a single IVT injection every 4 weeks.

Selection and timing of dose for each subject

Subjects were randomized by IWRS to receive 13 doses of either Rimmyrah or Lucentis in the study eye by ophthalmic IVT injection once every 4 weeks (approximately 28 days) over a treatment period of 48 weeks. The safe minimum interval between 2 consecutive doses was not to be less than 21 days considering the visit window period.

Investigational and reference products (Rimmyrah and Lucentis) are administered only by qualified ophthalmologists experienced in IVT injections. The injections are administered under controlled aseptic conditions, including the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide are given before the injection.

Subjects were monitored onsite before and after each injection for at least 60 minutes to assess any treatment toxicities and to perform appropriate management if needed. Approximately 30 (±10) minutes after the IVT injection, subjects were monitored for elevation in IOP using tonometry.

Objectives

Primary objective

The primary objective of the study was to demonstrate that the biosimilar candidate Rimmyrah is equivalent to Lucentis (ranibizumab) in subjects with wet (neovascular) age-related macular degeneration (wAMD).

Secondary Objectives

• To evaluate the efficacy of Rimmyrah versus Lucentis in subjects with wAMD based on central foveal thickness (CFT), area of CNV, and leakage from CNV lesion.

• To evaluate the systemic exposure of Rimmyrah versus Lucentis in subjects participating in PK evaluation.

• To evaluate the safety of Rimmyrah versus Lucentis.

• To evaluate immunogenicity of Rimmyrah versus Lucentis.

Outcomes/endpoints

Primary efficacy endpoint

The primary endpoint was the change in BCVA letters at Week 8 compared to baseline in the study eye using the ETDRS protocol.

The chosen primary endpoint of change in BCVA letters from baseline at Week 8 (ETDRS letters) is a validated and sensitive functional endpoint and was agreed on by CHMP during the prior SA procedure.

Secondary efficacy endpoints

• Change in CFT at Week 2, Week 4, Week 8, Week 16, Week 24, and Week 52 compared to baseline in the study eye, as measured by optical coherence tomography (OCT). CFT measurement is the key secondary variable, with special focus on Central Subfield Thickness

• Change in BCVA letters over the course of the study compared to baseline in the study eye using the ETDRS protocol

• Change in total size of CNV leakage area at Week 24 and Week 52 compared to baseline in the study eye, as measured by fluorescein angiography (FA)

• Change in total size of CNV at Week 24 and Week 52 compared to baseline in the study eye, as measured by FA

• Percentage of subjects with loss of $\leq$15 letters using ETDRS, evaluated as change at Week 8, Week 24, and Week 52 compared to baseline in the study eye

• Percentage of subjects with gain of >15 letters using ETDRS, evaluated as change at Week 8, Week 24, and Week 52 compared to baseline in the study eye

• Change in intra- or sub-retinal fluid status measured by OCT in the study eye

• Number of subjects without intra- or sub-retinal fluid at Week 24 and Week 52 in the study eye

• Number of subjects with retinal pigment epithelium detachments in the study eye

Secondary efficacy endpoints comprise anatomical and functional parameters and are considered overall appropriate for this biosimilarity trial comparing Rimmyrah to EU-Lucentis.

PK endpoint

Maximum observed concentration at certain time points.

Immunogenicity endpoint

Immunogenicity (anti-ranibizumab antibodies, antidrug antibody [ADA], and neutralizing ADA [NAb]) measurement before treatment at Day 1, Week 4, Week 8, Week 12, Week 24, and Week 52. Additional samples for monitoring of immunogenicity are to be collected from subjects with any signs of intraocular inflammation, as these might indicate an immune reaction.

Safety endpoints:

• Adverse events (AEs), as defined by treatment-emergent AEs (TEAE), SAE, related TEAE, and related SAE

• Injection site reactions

• Intraocular inflammation

• Systemic treatment (Rimmyrah or Lucentis) concentrations at Week 20

• Laboratory parameters (hematology, clinical chemistry, urinalysis, vital signs, etc.)

• Intraocular pressure (IOP) and perfusion of the optic nerve

• Ophthalmological examinations

• Other safety assessments (FA, OCT, IOP, slit-lamp examination [SLE], and dilated fundus examination)

Sample size

From a weighted pooled analysis of 5 studies of Lucentis in wAMD population, the mean change from Baseline in BCVA for Lucentis was approximately 6.6 letters, with an SD of 10.4 letters.

Assuming an SD of 10.4 for Lucentis at Week 8, a true hypothesised treatment difference of 0, alpha of 0.025 (ie, a 2-sided 95% confidence interval) and an equivalence range for the difference in BCVA letters of [-3.49, +3.49], at least 232 randomised subjects per treatment group (464 subjects) were planned to provide approximately 90% power to ascertain the efficacy equivalence of Rimmyrah versus Lucentis with respect to the primary endpoint. Allowing for a 20% dropout, at least 290 subjects per treatment group (580 subjects) were to be randomised.

Table 16. The BCVA Improvement Responses in Pivotal Studies of Lucentis

Study	N	BCVA Change at Week 8	Standard Error	Estimated SD
ANCHOR (NCT00061594)	140	9.8	1	11.83215957
MARINA (NCT00056836)	240	5.4	0.6	9.295160031
HARBOR (NCT00891735)	275	7.69	0.599	9.933291247
SAILOR (NCT00251459)	490	5.8	0.5	11.06797181
EXCITE (NCT00275821)	118	6.5	0.82	8.907480003
Pooled	**1263**	**6.64**		**10.367**

Source: Section 5.3.3.5.1 Protocol QL1205-002.

[Table 16: Table 2.7.3-1 from Summary of Clinical Efficacy]

The sample size is in principle acceptable, and the sample size considerations and assumptions are comprehensible. The margin is discussed elsewhere.

The sample size was changed in protocol version 4, when the sample size of 580 was already reached. Previous to protocol version 4 it was planned to enrol 656 subjects. However, the applicant assured that changes to the study design were made without knowledge of the primary outcome and that the respective study personnel was blinded.

Randomisation and blinding (masking)

Upon confirmation of eligibility for a given subject to participate in the study, a unique randomization number for that subject was assigned via IWRS. The IWRS was accessed immediately by study site personnel after confirmation of the subject's eligibility had been recorded.

The randomization scheme included the following stratification parameters to ensure balanced distribution of assignment to the 2 treatments: geographical region where enrolled (China/India vs. Europe) and the BCVA letters at Baseline (≦ 66 letters vs. > 66 letters). Permuted random blocks within each stratification combination were used to ensure the 1:1 ratio within each combination.

An independent biostatistician created the randomization scheme, which was planned to remain s unavailable to all other masked individuals until after study completion and subsequent locking of the study database.

Central randomization is endorsed. The stratification by two two-level factors seems feasible with the given sample size.

The study was blinded. Due to the study objectives, the identity of the study treatment assignments was not known to subjects. Additionally, except for the site designees who were unmasked for the purpose of preparing and administering the study treatments, other research staff was also masked. Masked study team members perform efficacy assessments.

There was no overlap between the masked and unmasked staff members. Access to the randomization code(s) was strictly controlled.

The test product and the reference product may have caps/stoppers of differing colors and length; however, they were packaged and labeled in identical outer cartons. Therefore, sites had to have the following unmasked team members and their designated back-ups:

• Unmasked personnel prepare syringe(s) for IVT injection and provide to the unmasked injector, and complete test product accountability

• Unmasked injector performs injection and safety assessments immediately after the injections (but do not participate in the efficacy assessments)

• There were also masked and unmasked clinical research associates available for the same site. Unmasked clinical research associates monitored drug accountability

Randomization information for any particular subject were made available to the investigator only in the event of a medical emergency or an AE that necessitated identification of the study drug for the welfare of that subject. Masking codes were only to be broken in emergency situations for reasons of subject safety. Whenever necessary, the investigator(s) was to consult with the Medical Monitor and the Sponsor before breaking the masking, but it was possible for the investigator to unmask the study treatment by himself/herself without contacting the Sponsor/Medical Monitor.

When the masking code was broken, the reason was to be fully documented. The reporting requirements for unmasking were the same for reporting an SAE.

To maintain the study masking at the study site(s), the bioanalytical laboratory staff who analyzed the PK and immunogenic (ie, anti-ranibizumab antibodies, ADA, and NAb) samples were masked.

The study masking is broken upon completion of the study and after the study database has been locked for the final analysis.

When all subjects had completed their 6-month assessments, an unmasked analysis of efficacy (the primary analysis of efficacy) was performed.

Blinding is endorsed.

There may have been a risk of unblinding due to differences in caps/stoppers between the products. It is acknowledged that the applicant took measures to reduce the risk of unblinding (i.e. additional unblinded personnel).

Statistical methods

Analysis sets:

The Full Analysis population (FAS) was planned to consist of all randomized subjects who receive at least 1 dose of study drug.

The Per-protocol population with regards to the primary endpoint was planned to consist of all subjects in the FAS for whom no major protocol deviations affecting the primary efficacy endpoints occurred during the course of the study.

The Safety Analysis population (SAF) was planned to consist of all randomized subjects who received at least 1 administration of study drug. On the SAF, all subjects were planned to be analyzed under the actual treatment received.

The PK Analysis population was planned to consist of all subjects in SAF with at least 1 evaluable postbaseline PK measurement.

Hypotheses

The statistical hypothesis associated with the primary analysis of change in BCVA letters at Week 8 was planned to be:

H0: The difference in the change of BCVA letters from Baseline to Week 8 in the study eye between the 2 treatment groups is less than -3.49 letters or greater than 3.49 letters;

versus

H1: The difference in the change of BCVA letters from Baseline to Week 8 in the study eye between the 2 treatment groups is within the range [-3.49, +3.49] letters.

Analysis

The change in BCVA letters at Week 8 compared to Baseline in the study eye using the standard ETDRS protocol was planned to be analyzed as the difference between Rimmyrah and Lucentis® (Rimmyrah minus Lucentis®) at Week 8. For this endpoint, equivalence was planned to be declared if the 2-sided 95% CI around the difference between the treatments of the change from Baseline in ETDRS letters at Week 8 lies entirely within the range [-3.49, +3.49].

The primary efficacy endpoint was planned to be analyzed using a repeated measures analysis of covariance model with factors treatment arm (Rimmyrah versus Lucentis; reference Lucentis), visit and treatment*visit interaction and any stratification factors. The estimate of the least-squared means, difference, and the 95% CI for the difference were planned to be presented.

This primary analysis was to be conducted on the FAS. For this analysis, any subjects with missing data at Week 8 was planned to be imputed using a method of multiple imputation.

The primary analysis was planned to be repeated on the Per-protocol Set as a sensitivity measure.

In the SAP, Draft v2.0 21st January 2022, estimands and strategies for handling of intercurrent events were defined (for the primary endpoint):

Table 17

	Primary Estimand	Secondary Estimand	Tertiary Estimand
Treatment conditions of interest	QL1205 vs Lucentis®	QL1205 vs Lucentis®	QL1205 vs Lucentis®
	Test: QL1205 (ranibizumab biosimilar, 10 mg/mL) Reference: Lucentis® (ranibizumab, 10 mg/mL)	Test: QL1205 (ranibizumab biosimilar, 10 mg/mL) Reference: Lucentis® (ranibizumab, 10 mg/mL)	Test: QL1205 (ranibizumab biosimilar, 10 mg/mL) Reference: Lucentis® (ranibizumab, 10 mg/mL)
Population	Subjects with Neovascular Wet Age-related Macular Degeneration (wAMD).	Subjects with Neovascular Wet Age-related Macular Degeneration (wAMD).	Subjects with Neovascular Wet Age-related Macular Degeneration (wAMD).
Endpoint	Change from baseline to Week 8 in BCVA as measured by ETDRS letter score in the study eye.	Change from baseline to Week 8 in BCVA as measured by ETDRS letter score in the study eye.	Change from baseline to Week 8 in BCVA as measured by ETDRS letter score in the study eye.
Population level summary	Difference between treatments in mean change from baseline in BCVA in the study eye at Week 8.	Difference between treatments in mean change from baseline in BCVA in the study eye at Week 8.	Difference between treatments in mean change from baseline in BCVA in the study eye at Week 8.
ICEs and strategies to handle ICEs	• Death prior to assessment of BCVA *Composite strategy* • Premature discontinuation of study treatment for reason of "AE", "LoE" or "Need for Rescue Medication" *Composite strategy* • Premature discontinuation of study treatment for reason other than "AE", "LoE" or "Need for Rescue Medication" *Hypothetical strategy* • Missed data due to COVID *Treatment policy strategy*	• Death prior to assessment of BCVA *Composite strategy* • Premature discontinuation of study treatment for reason of "AE", "LoE" or "Need for Rescue Medication" *Composite strategy* • Premature discontinuation of study treatment for reason other than "AE", "LoE" or "Need for Rescue Medication" *Treatment Policy strategy* • Missed data due to COVID *Treatment policy strategy*	• Death prior to assessment of BCVA *Composite strategy* • Premature discontinuation of study treatment for reason of "LoE" *Composite strategy* • Premature discontinuation of study treatment for reason other than "LoE" *Treatment Policy strategy* • Missed data due to COVID *Treatment policy strategy*
	ICE(s) with a composite variable strategy take priority over ICEs with other strategies.		

The handling of intercurrent events was defined as follows:

Composite variable strategy: data following the intercurrent event were planned to be set to missing and were to be imputed using a return-to-baseline MI approach.

Treatment policy strategy: Available data occurring on or after the ICE was to be analyzed as observed. Missing BCVA assessment were planned to be imputed by an MAR application of SAS Proc MI.

Hypothetical strategy: Available data occurring on or after the ICE was planned to be set to missing, and multiple imputed by a missing not at random (MNAR) method.

Overall the methods do not raise any strong concerns. However, it is noted that several important details were not specified in the study protocol, including the primary estimand, missing data handling and details of the longitudinal analysis model, such as the covariance structure matrix. This is not ideal and consistency of several analyses will be required to provide reassurance that results are robust against lack of prespecification of relevant details.

Margin

Initially a margin of ±3 was planned and the margin was increased to ±3.49 in protocol version 4. This was discussed in Scientific Advice, but in contrary to the applicant's statement in the overview, the margin of ±3.49 was not endorsed. Rather the final advice letter stated that "CHMP recommends that the margin remains lower than ±3.5 letters". ±3.49 only artificially fulfils this recommendation. No sound clinical or statistical justification for the margin was provided in the study protocol. However, a margin of ±3.5 has been accepted for very similar applications.

Analysis population

The analysis population (FAS) is acceptable, consistency of results in the FAS and PP is a prerequisite for the conclusion of equivalent efficacy.

Intercurrent events

In principle, it is endorsed that different strategies for the handling of intercurrent events are presented. However, it is noted that the respective strategies were only defined in the SAP, dated 21 January 2022.

The primary estimand includes a composite strategy for death and for discontinuation of study medication due to AE, LoE or need for rescue medication. This composite strategy is addressed in the analysis by a return to baseline approach in which measurements after the intercurrent event are supposed to be shifted towards the baseline values. Although a composite strategy may in principle be acceptable, the analysis is not necessarily considered appropriate for an equivalence trial: The imputation seems to omit treatment allocation and thus impute under the alternative hypothesis of no difference between the two treatments.

The primary estimand includes a hypothetical strategy for intercurrent events related to the covid-19 pandemic and for discontinuation of study treatment for reasons not related to AE, LoE or need for rescue medication. This strategy is addressed by imputing data following the intercurrent event, based on the distribution of those patients who did not experience the intercurrent event. This might be a reasonable approach in some situations.

Relevant intercurrent events were defined in the SAP. The applicant was asked to discuss whether there were any imbalances in the distribution of those intercurrent events between the two treatment arms. With his responses to the D120 LoQ, he provided information on the incidence of those intercurrent events that were specified in the study protocol. It is agreed that the incidence is small and that there are no strong imbalances.

There was uncertainty with respect to the composite and hypothetical strategy for intercurrent events and with regard to handling of missing data. These aspects were not defined in the study protocol and it is not obvious how the analysis details may affect the interpretation (e.g. the composite strategy seems to impute under the alternative of no difference between the two treatments). In order to rule out uncertainty the applicant was asked to present a simple analysis using all data as observed (i.e. a treatment policy strategy for all intercurrent events) complemented by a tipping-point analysis for any

missing values. The applicant provided sensitivity analyses as requested. In short, results were reassuring. The tipping-point analyses suggest that in the ITT set a tipping-point for equivalence (i.e. tipping-point at which the 95% CI is no longer included in ±3.49) in the imputation of missing values on top of a simple treatment policy analysis lies somewhere around a ≥12 point difference in favour of Lucentis or a ≥40 point difference in favour of Rimmyrah, this is observed across several scenarios. In the PP set the tipping-points are further away from no difference. In light of the observed change from baseline in BCVA in either treatment group, these scenarios appear highly unlikely. Thus, the tipping-point analyses provided good reassurance that results are robust.

It was noted that a number of doses were skipped due to COVID-19 related restrictions. Skipping doses is expected to reduce the effect of either treatments, hence the treatment policy strategy for covid-19 related intercurrent events may shift the estimate towards no difference and may be anti-conservative. During the procedure, the applicant provided results of an analysis in which a hypothetical strategy was chosen for skipped doses due to COVID-19. In this analysis data after the intercurrent event (skipped dose) was set to missing and imputed with multiple imputation, based on the distribution of those participants who did not experience the intercurrent event. This appears plausible.

Significance level and multiplicity

The approach via a two-sided 95% confidence interval to be entirely included in the margin is reasonable and endorsed. There is only one primary analysis and hence multiplicity is not an issue.

Analysis model

The planned repeated measured ANCOVA is acceptable. Some technical details such as the covariance structure matrix (unstructured) were only specified in the SAP.

Missing data handling

In the study protocol there are conflicting statements on missing data handling (section 11.3.8: no imputation vs. section 11.3.3.1: multiple imputation), eventually a MI approach was applied. This raises some uncertainty; however it is acknowledged that a sensitivity analysis without imputation provides reassurance. Further, a tipping point analysis was presented suggesting that results are robust against violation of the underlying MAR assumption.

Interim analysis

The primary analysis was planned to be conducted during the ongoing study, when all patients had the opportunity to be followed up for 24 weeks. This may pose a risk to the integrity of the ongoing trial despite measures taken by the applicant. The interpretation of any later analyses may require additional care. However, this does not affect the primary endpoint which is measured at week 8.

Results

Participant flow

A total of 919 subjects were screened, of whom 616 subjects were randomized 1:1 to Rimmyrah and Lucentis (308 subjects each). Of the 616 randomized subjects, 594 subjects (96.4%) completed the study treatment up to Week 24 per protocol while 22 subjects (3.6%) did not.

The main reason for not completing the study treatment up to Week 24 per protocol was subject withdrawal of consent (9 subjects, 1.5%), followed by AE and other reasons (5 subjects each, 0.8%). Of the 616 randomized subjects, 44 subjects (7.1%) discontinued the study prematurely as of the data cutoff of 27 Jan 2022, mainly because of withdrawal of consent (18 subjects, 2.9%), followed by AE and other reasons (10 subjects each, 1.6%).

Table 18. Subject Disposition – Screened Set

	QL1205	Lucentis	Total
Subjects screened			919
Screen failures			303 (33.0%)
Primary reason for screen failure			
Adverse event			3 (0.3%)
Lost to follow-up			2 (0.2%)
Other			26 (2.8%)
PI decision			4 (0.4%)
Sponsor decision			1 (0.1%)
Subject did not fulfill all eligibility criteria			228 (24.8%)
Subject withdrew consent			39 (4.2%)
Eligible subjects randomized	304 (98.7%)	304 (98.7%)	608 (98.7%)
Non eligible subjects randomized	4 (1.3%)	4 (1.3%)	8 (1.3%)
Total randomized subjects	308 (100%)	308 (100%)	616 (100%)
Subject completed the treatment up to W24 as per protocol, Yes	298 (96.8%)	296 (96.1%)	594 (96.4%)
Subject completed the treatment up to W24 as per protocol, No	10 (3.2%)	12 (3.9%)	22 (3.6%)
Primary reason for discontinued/withdrawal from study treatment			
Adverse event	3 (1.0%)	2 (0.6%)	5 (0.8%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	2 (0.3%)
Other	1 (0.3%)	4 (1.3%)	5 (0.8%)
Sponsor request	0	1 (0.3%)	1 (0.2%)
Withdrawal of consent	5 (1.6%)	4 (1.3%)	9 (1.5%)
Subject discontinued the study prematurely, Ongoing	57 (18.5%)	53 (17.2%)	110 (17.9%)
Subject discontinued the study prematurely, No	234 (76.0%)	228 (74.0%)	462 (75.0%)
Subject discontinued the study prematurely, Yes	17 (5.5%)	27 (8.8%)	44 (7.1%)
Primary reason for study discontinuation			
Adverse event	5 (1.6%)	5 (1.6%)	10 (1.6%)
Lost to follow-up	2 (0.6%)	4 (1.3%)	6 (1.0%)
Other	3 (1.0%)	7 (2.3%)	10 (1.6%)
Withdrawal of consent	7 (2.3%)	11 (3.6%)	18 (2.9%)

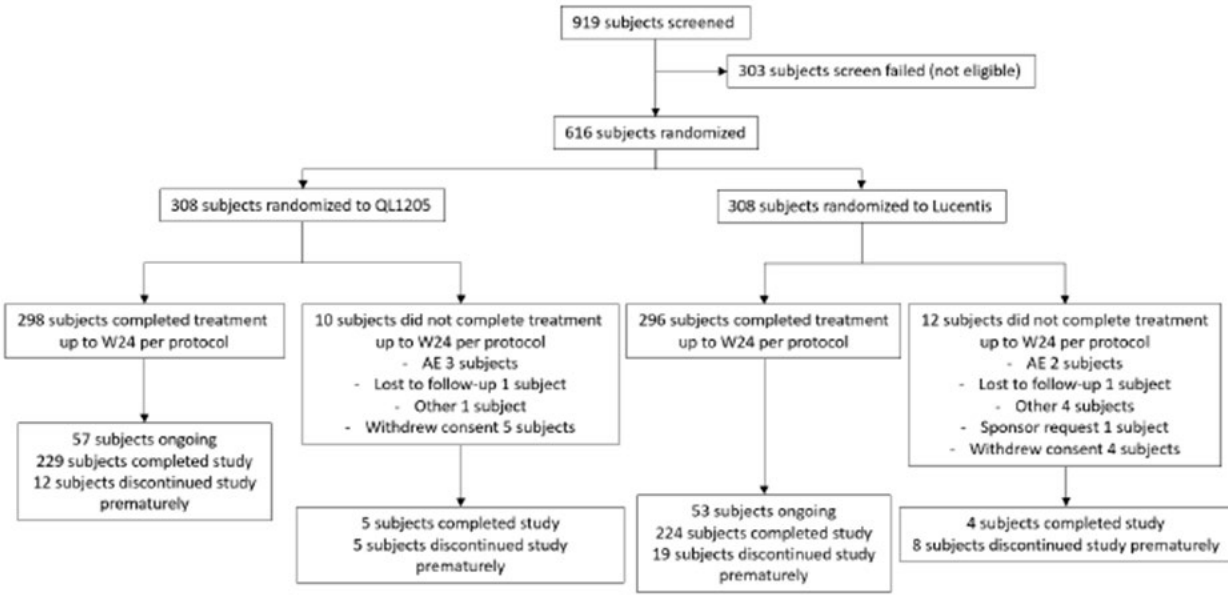
Abbreviations: PI, Principal Investigator; W, Week.

Note: Screen failures (with reasons), randomization and dosing with study drug were summarized for the Screened Set. Study completion and early termination (with reasons) as well as attendance at each visit were summarized for the ITT.

Source: Table 14.1.1.1

[Table 18: Table 5 from Interim CSR]

Figure 3. Subject Disposition



Abbreviations: AE, adverse event; W, Week.
Source: Table 14.1.1.1 and Listing 16.2.1.1

[Figure 3: Figure 2 from Interim CSR]

Overall, 594 subjects (96.4%) completed the study treatment up to Week 24 (primary EP analysis). The number of patients who completed the study were comparable between treatment arms (96.8% vs 96.1%).

The most common reasons for premature study discontinuation (until DCO in January 2022) were consent withdrawal, adverse events and "other reasons". 3 patients in the Rimmyrah arm and 7 patients in the EU-Lucentis arm discontinued the study prematurely due to "other reasons" until DCO. During the procedure, the applicant clarified the "other" reasons leading to premature study discontinuation until DCO for IA. Those reasons were mainly the COVD-19 pandemic, death, refusal to visit or to continue, as well as "personal" reasons. Furthermore, an updated subject disposition table has been provided with the final updated CSR, with all randomized participants included (final data set). Here, an exhaustive list of the reasons for premature study discontinuation is included. No notable differences or imbalances between the treatment arms were noted.

Discontinuation of study treatment due to lack of efficacy is one of the major intercurrent events specified in the SAP. However, it was confirmed by the applicant that lack of efficacy was not reported as leading reason for discontinuation.

Recruitment

Study Start: 27 June 2019

Study Completion Date: not yet reached (at the DCO for the Interim CSR, which was the 27 January 2022, 110 participants were still ongoing in the study)

The study was conducted at a total of 75 sites in 11 EU countries, as well as in Ukraine, Russia and Israel.

Conduct of the study

Changes in the conduct of the study

Overall, three protocol amendments were done. Brief summaries of the amendments are as follows:

• Version 1 (16 Nov 2018) to Version 2 (21 Dec 2018): amendments made to address EMA Scientific Advice feedback, including change of total lesion area in eligibility criterion from ≤12.0 DA to ≤9.0 DA, rearrangement of secondary endpoints, and removal of requirement on pregnant partner consent form.

• Version 2 to Version 3 (10 Nov 2020): Added minor clarifications to eligibility criteria, visit windows, and assessments; added laboratory tests for eligibility at the investigator' s discretion; and added information from the completed QL1205-001 study.

• Version 3 to Version 4 (04 Jun 2021): sample size updated (from approximately 656 to at least 580 subjects to be enrolled and randomized) and corresponding information added (such as update of equivalence margin for primary endpoint from [-3.0, +3.0] to [-3.49, +3.49]). Updates made to the country-specific Czech Republic protocol were also added into the main protocol.

Changes to the Planned Analyses

The SAP v2.0 (dated 21 Jan 2022) included the following changes to the analysis planned in the protocol: expansion of the following sections to account for the ICH E9 (R1) guidance on estimands and sensitivity analyses.

• Missing data section to include items for MAR and MNAR and added in the planned imputation methods.

• Addition of 3 estimands for the primary endpoint analysis and also a sensitivity analysis and a supportive analysis for the primary endpoint.

Minor changes in the population labels were as follows: Enrolled population is now Screened Set and full analysis population is now Intent-to-Treat Set.

Minor changes to the planned analyses for this interim analysis were as follows:

• Categorization of AEs into all, study eye, fellow eye, and non-ocular.

• Efficacy analysis by BCVA letters at Baseline (post-hoc).

Among the changes to the planned analyses, some are substantial.

The increase of the equivalence margin is considered to reflect that there was no good understanding of what constitutes a clinically irrelevant difference at the initial planning of the study. It is noted that no discussion of clinical irrelevance was presented in the study protocol for the wider margin and consequently there remains some uncertainty.

The approach to intercurrent events substantially changes the analysis. Thus, the late definition of estimands in the SAP and not in the study protocol adds uncertainty.

Both aspects are discussed in more detail in the discussion on clinical efficacy and have been satisfactorily addressed by the applicant as detailed below.

Baseline data

Table 19. Demographic and Baseline Characteristics – ITT Set

	QL1205 (N=308)	Lucentis (N=308)	Total (N=616)
Age (years)[a]			
Mean (SD)	70.5 (9.47)	72.2 (8.73)	71.4 (9.14)
Median	71.0	72.0	72.0
Min, Max	50, 94	50, 93	50, 94
Gender, n (%)			
Male	157 (51.0)	147 (47.7)	304 (49.4)
Female	151 (49.0)	161 (52.3)	312 (50.6)
Gender by Age Category, n (%)			
Male			
Age 50-60	31 (10.1)	10 (3.2)	41 (6.7)
Age 61-70	59 (19.2)	54 (17.5)	113 (18.3)
Age >70	67 (21.8)	83 (26.9)	150 (24.4)
Female			
Age 50-60	23 (7.5)	14 (4.5)	37 (6.0)
Age 61-70	38 (12.3)	51 (16.6)	89 (14.4)
Age >70	90 (29.2)	96 (31.2)	186 (30.2)
Ethnicity, n (%)			
Hispanic or Latino	12 (3.9)	12 (3.9)	24 (3.9)
Not Hispanic or Latino	293 (95.1)	295 (95.8)	588 (95.5)
Not Reported	3 (1.0)	1 (0.3)	4 (0.6)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.3)	1 (0.2)
Asian	124 (40.3)	125 (40.6)	249 (40.4)
White	184 (59.7)	182 (59.1)	366 (59.4)
Race by Age Category, n (%)			
American Indian or Alaska Native			
Age >70	0	1 (0.3)	1 (0.2)
Asian			
Age 50-60	39 (12.7)	18 (5.8)	57 (9.3)
Age 61-70	49 (15.9)	55 (17.9)	104 (16.9)
Age >70	36 (11.7)	52 (16.9)	88 (14.3)
White			
Age 50-60	15 (4.9)	6 (1.9)	21 (3.4)
Age 61-70	48 (15.6)	50 (16.2)	98 (15.9)
Age >70	121 (39.3)	126 (40.9)	247 (40.1)
Height (cm)			
Mean (SD)	164.50 (9.541)	163.82 (9.373)	164.16 (9.456)
Median	165.00	164.00	164.75
Min, Max	134.0, 190.0	134.0, 191.0	134.0, 191.0
Weight (kg)			
Mean (SD)	72.60 (14.023)	71.54 (14.563)	72.07 (14.294)
Median	72.00	70.00	71.00
Min, Max	33.6, 119.0	40.0, 130.0	33.6, 130.0
BMI (kg/m^2)			
Mean (SD)	26.79 (4.580)	26.63 (4.802)	26.71 (4.689)
Median	26.10	26.35	26.20
Min, Max	16.2, 43.3	15.5, 50.2	15.5, 50.2

Abbreviations: BMI, body mass index; ITT, Intent-to-Treat population; Max, Maximum; Min, Minimum; N, number of subjects; n, number of subjects in the specified category; SD, standard deviation
Note: Percentages were calculated based on the number of subjects in the ITT Set.
a Age at time of consent.
Source: Table 14.1.3.1.1

The mean (SD) age was 70.5 (9.47) years in the Rimmyrah and 72.2 (8.73) years in the Lucentis treatment arm. There were numerically more male and more female patients in the Lucentis arm belonging to the age category >70 years than in the Rimmyrah (male: n=83 versus n=67; female: n=96 vs n=90).

A tabulated summary of the study population per treatment arm by age, including the age categories ≤75 years as well as >75 years, has been provided during the procedure, as requested. Comparable numbers of patients with an age >75 years were included in both study arms.

Table 20. Demographic and Baseline Characteristics - ITT Set

	QL1205 (N=308)	Lucentis (N=308)
Age (years)		
Mean (SD)	70.5 (9.47)	72.2 (8.73)
Median	71.0	72.0
Min, Max	50, 94	50, 93
Age category, n %)		
Age ≤75	207 (67.2)	195 (63.3)
Age >75	101 (32.8)	113 (36.7)

Ref. Table 8 (source: Table 14.13.1.1) of final updated QL1205-002 CSR

In the Rimmyrah treatment arm, 157 (51.0%) patients were male, and 151 (49.0%) patients were female. In the Lucentis treatment arm, 147 (47.7%) patients were male, and 161 (52.3%) patients were female. The mean Body Mass Index (BMI) was 26.79 kg/m2 in the Rimmyrah and 26.63 kg/m2 in the Lucentis treatment arm. Majority of the patients were White (59.7% in the Rimmyrah and 59.1% in the Lucentis treatment arm) or Asian (40.3% in the Rimmyrah and 40.6% in the Lucentis arm). Overall, there are no concerns regarding demographics.

Table 21. Ocular Baseline Characteristics – ITT Set

	QL1205 (N=308)	Lucentis (N=308)
Best corrected visual acuity		
Mean (SD)	55.6 (11.86)	55.1 (12.19)
Median	57.0	56.0
Min, Max	34, 86	30, 74
95% CI	54.2 - 56.9	53.7 - 56.4
Central foveal thickness (µm)		
Mean (SD)	374.2 (139.98)	367.9 (132.67)
Median	348.0	344.0
Min, Max	130, 1053	132, 967
95% CI	358.4 – 390.0	353.0 – 382.9
Total size of CNV leakage area (mm^2)		
Mean (SD)	7.90 (5.596)	7.57 (5.245)
Median	6.65	6.20
Min, Max	0.4, 41.1	0.2, 27.5
95% CI	7.27 – 8.53	6.98 – 8.16
Total CNV (mm^2)		
Mean (SD)	6.0 (4.73)	5.9 (4.69)
Median	5.0	5.0
Min, Max	0, 21	0, 22
95% CI	5.5 – 6.6	5.4 – 6.4

Abbreviations: CI, confidence interval; CNV, choroidal neovascularization; ITT, Intent-to-Treat population; Max, Maximum; Min, Minimum; N, number of subjects; SD, standard deviation.
Note: For central foveal thickness, the number of subjects at Baseline was 305 in each group.
Source: Table 14.2.1.1.1, Table 14.2.2.3.1, Table 14.2.2.2.1, Table 14.2.2.2.3

Baseline disease characteristics with regard to BCVA, CFT, and CNV have been presented by the applicant and are overall comparable between the treatment arms.

Table 22. Demographic and Baseline Characteristics – ITT Set

	QL1205 (N=308)	Lucentis (N=308)
Time since first diagnosis of neovascular AMD (weeks)		
Mean (SD)	9.5 (21.93)	12.3 (47.26)
Median	4.0 (3.0, 7.0)	3.5 (2.0, 7.0)
Min, Max	1, 171	1, 577

Ref. Table 8 (source: Table 14.1.3.3.5) of final updated QL1205-002 CSR

The mean duration (in weeks) since first diagnosis was longer in the Lucentis group than in the Rimmyrah group (12.3 ± 47.26 weeks vs. 9.5 ± 21.93 weeks). This imbalance was attributed to the presence of outliers with long duration of disease, which was more present in the Lucentis than in the Rimmyrah arm. In the Lucentis arm, there were 2 patients included with more than 500 weeks from first diagnosis to study BL. This explanation is considered reasonable.

Medical history

Ophthalmic Medical History

Most subjects (552 subjects, 89.6%) had ophthalmic medical history. Overall, medical histories reported by ≥5.0% of subjects included cataract (330 subjects, 53.6%), dry age-related macular degeneration (207 subjects, 33.6%), astigmatism (168 subjects, 27.3%), cataract nuclear (77 subjects, 12.5%), cataract cortical (59 subjects, 9.6%), hypermetropia (59 subjects, 9.6%),

intraocular lens implant (38 subjects, 6.2%), retinal drusen (36 subjects, 5.8%), and neovascular age-related macular degeneration (31 subjects, 5.0%).

Most subjects (509 subjects, 82.6%) had ophthalmic medical history in the study eye. Overall, medical histories reported by ≥5.0% of subjects included cataract (321 subjects, 52.1%), astigmatism (140 subjects, 22.7%), cataract nuclear (67 subjects, 10.9%), cataract cortical (54 subjects, 8.8%), hypermetropia (52 subjects, 8.4%), and intraocular lens implant (34 subjects, 5.5%) in the study eye.

Overall, a comparable number of patients in the Rimmyrah (80.5%) and Lucentis (84.7%) treatment arms had an ophthalmologic history in the study eye ongoing at screening.

Non-Ophthalmic Medical History

Most subjects (530 subjects, 86.0%) had non-ophthalmic medical history. The most frequent non-ophthalmic medical histories by SOC were vascular disorders (395 subjects, 64.1%), metabolism and nutrition disorders (251 subjects, 40.7%), and cardiac disorders (147 subjects, 23.9%). The most frequent non-ophthalmic medical histories by PT were hypertension (374 subjects, 60.7%), type 2 diabetes mellitus (112 subjects, 18.2%), and hypercholesterolaemia (63 subjects, 10.2%).

The number of patients in the Rimmyrah and Lucentis treatment arms who had a non-ophthalmic medical history was comparable (264 [85.7%] patients in Rimmyrah and 266 [86.4%] patients in the Lucentis treatment arms), with medical history reported most frequently in the SOC Vascular disorders, PT Hypertension (n=191 [62.0%] versus n=183 [59.4%]).

Prior medications

Prior medications were used only by few study participants (QL1205: n=31 [10.0%], Lucentis: n=21 [6.8%]). As prior medications, predominantly ophthalmologics were used.

Concomitant medications

Overall, the use of concomitant medications was reported for most patients of the SAF (QL1205: n=285, Lucentis: n=279). Concomitant medications included predominantly antithrombotic agents, lipid-modifying agents and thyroid therapies. The most frequently used concomitant medications in the study eye were antiinfectives. The use of concomitant medications was overall balanced between treatment arms.

Treatment compliance

Compliance up to Week 8 was 97.4% in the Rimmyrah group and 98.5% in the Lucentis group. Compliance up to Week 24 was 99.01% in the Rimmyrah group and 99.27% in the Lucentis group. There were no notable differences in treatment compliance between the 2 groups.

Table 23. Treatment Compliance – Safety Set

	QL1205 (N=309)	Lucentis (N=307)
Compliance up to Week 8		
n	309	307
Mean (SD)	97.4 (11.10)	98.5 (8.45)
Median	100.0	100.0
Min, Max	50, 100	50, 100
Compliance up to Week 24		
n	309	307
Mean (SD)	99.01 (5.849)	99.27 (3.943)
Median	100.00	100.00
Min, Max	42.9, 100.0	60.0, 100.0

Abbreviations: Max, Maximum; Min, Minimum; N, number of subjects; n, number of subjects in the specified category; SD, standard deviation

Note: Compliance up to Week 8 = (number of actual doses administered/number of planned doses)*100%, up to and including Week 4.

Compliance up to Week 24 = (number of actual doses administered/number of planned doses)*100%, up to and including Week 24.

Source: Table 14.1.5.1

[Table 23: Table 10 from Interim CSR]

Numbers analysed

All 616 randomized subjects received at least 1 dose of study drug and were included in the **ITT Set** (n=308 per arm). Regardless of region, majority had a baseline BCVA of ≤66 letters (471/616 subjects, 76.5%).

Of the 616 randomized subjects, 568 subjects (284 subjects in each group, 92.2%) were included in the **PP Set**. Reasons for exclusion from the PP Set are provided in Table 24 below. The most common reasons for exclusion were non-compliance with study drug (QL1205: 13 subjects, 4.2%; Lucentis: 9 subjects, 2.9%), major protocol deviation affecting efficacy analysis (QL1205: 4 subjects, 1.3%; Lucentis: 6 subjects, 1.9%), and outside visit window (QL1205: 1 subject, 0.3%; Lucentis: 7 subjects, 2.3%).

All 616 randomized subjects were included in the **Safety Set**. One subject randomized to Lucentis was included under the Rimmyrah group in the Safety Set (Listing 16.2.2.1): Subject was administered an incorrect investigational medicinal product kit at Day 1 visit because of site error (ie, randomized to Lucentis but received QL1205); the subject was subsequently discontinued from study treatment because of an SAE of stroke and did not receive any more doses (ie, only received 1 dose that was QL1205).

Thirty-three (10.7%) and 40 (13.0%) subjects in the Rimmyrah and Lucentis group, respectively, were included in the **PK Set**.

Table 24. Study Populations – ITT Set

	QL1205 (N=308)	Lucentis (N=308)
Subjects in the ITT Set	308 (100.0%)	308 (100.0%)
Subjects in ITT Set randomized on stratum:		
Region China/India – BCVA at Baseline ≤66 letters	100 (32.5%)	102 (33.1%)
Region China/India – BCVA at Baseline >66 letters	24 (7.8%)	23 (7.5%)
Region Europe - BCVA at Baseline ≤66 letters	136 (44.2%)	133 (43.2%)
Region Europe – BCVA at Baseline >66 letters	48 (15.6%)	50 (16.2%)
Subjects in the PP Set	284 (92.2%)	284 (92.2%)
Reason for exclusion of ITT subjects from PP		
Failed inclusion/exclusion criteria, noncompliance with study drug	1 (0.3%)	0
Failed inclusion/exclusion criteria, major PD affecting efficacy analysis	3 (1.0%)	1 (0.3%)
Major PD affecting efficacy analysis	4 (1.3%)	6 (1.9%)
Noncompliance with study drug	13 (4.2%)	9 (2.9%)
Noncompliance with study drug, major PD affecting efficacy analysis	1 (0.3%)	1 (0.3%)
Outside visit window	1 (0.3%)	7 (2.3%)
Prohibited medication	1 (0.3%)	0
Subjects in the Safety Set	309 (100.3%)	307 (99.7%)
Subjects in the PK Set	33 (10.7%)	40 (13.0%)

Abbreviations: BCVA, best corrected visual acuity; ITT, Intent-to-Treat population; N, number of subjects; PD, protocol deviation; PK, Pharmacokinetics; PP, Per Protocol.
Note: Percentages were calculated based on the number of subjects in the ITT Set.
Source: Table 14.1.2.2

The patient numbers analysed are overall balanced between the treatment arms Rimmyrah and EU-Lucentis.

The ITT population for the region "Europe" comprises 367 patients, 184 in the Rimmyrah arm and 183 in the EU-Lucentis comparator arm.

Outcomes and estimation

Primary endpoint analysis

Change from Baseline in BCVA at Week 8

The primary analysis for the change in BCVA letters at Week 8 compared to baseline in the study eye was conducted on the ITT (Intent-to-Treat Set) and was then repeated on the PPS (Per Protocol Set) as a sensitivity measure.

Table 25. Main Estimand – BCVA, Analysis at Week 8 – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
QL1205	308	6.08	0.561	(4.98, 7.18)	(5.16, 7.00)	
Lucentis	308	7.13	0.562	(6.03, 8.23)	(6.21, 8.05)	
QL1205 – Lucentis		-1.05	0.718	(-2.46, 0.36)	(-2.23, 0.13)	0.1434

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; ITT, Intent-to-Treat population; n, number of subjects in the specified category; SE, standard error.

Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm, the stratification factors region (China/India and Europe) and BCVA letters at Baseline (≤66 letters and >66 letters). Dependent variable being the change of BCVA letters from baseline in the study eye, equivalence was declared if the difference between the 2 treatment groups was within the range (-3.49, +3.49) letters.

Source: CSR QL1205-002 Table 14.2.1.1.7

In the ITT population, a mean change from baseline at Week 8 was 6.08 (95% CI: 4.98; 7.18) ETDRS letters for Rimmyrah and 7.13 (95% CI: 6.03; 8.23) ETDRS letters for EU-Lucentis. Biosimilarity was concluded, since the 95% CI of the adjusted treatment difference of -1.05 ETDRS letters was [-2.46; 0.36], which was completely contained within the predefined equivalence margin of ±3.49 letters.

Similar mean differences were observed for the PPS with 95% CIs within the predefined equivalence margin.

Table 26. Main Estimand – BCVA, Analysis at Week 8 – PP Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
QL1205	284	6.40	0.574	(5.27, 7.52)	(5.46, 7.34)	
Lucentis	284	7.25	0.573	(6.13, 8.38)	(6.31, 8.20)	
QL1205 – Lucentis		-0.85	0.730	(-2.29, 0.58)	(-2.06, 0.35)	0.2416

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; n, number of subjects in the specified category; SE, standard error.

Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm, the stratification factors region (China/India and Europe) and BCVA letters at Baseline (≤66 letters and >66 letters). Dependent variable being the change of BCVA letters from baseline in the study eye, equivalence was declared if the difference between the 2 treatment groups was within the range (-3.49, +3.49) letters.

Source: CSR QL1205-002 Table 14.2.1.1.8

Since both analysis sets, ITT and PPS, were fully contained within the pre-defined equivalence margin of ±3.49 letters, the study met its primary endpoint.

Analyses of the secondary and tertiary estimand (i.e. using different strategies for the intercurrent event of premature discontinuation of study treatment for reasons of "AE", "LoE", "Need for rescue medication" or other reasons) provide consistent results. This provides reassurance, although it should be noted that the intercurrent event strategies are not exhaustive, and other approaches may be reasonable as well.

Table 27. Secondary Estimand – BCVA, Analysis at Week 8 – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
QL1205	308	6.07	0.561	(4.97, 7.17)	(5.15, 6.99)	
Lucentis	308	7.13	0.561	(6.03, 8.23)	(6.21, 8.05)	
QL1205 – Lucentis		-1.06	0.717	(-2.46, 0.35)	(-2.24, 0.12)	0.1395

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; ITT, Intent-to-Treat population; n, number of subjects in the specified category; SE, standard error.

Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm, the stratification factors region (China/India and Europe) and BCVA letters at Baseline (≤66 letters and >66 letters). Dependent variable being the change of BCVA letters from baseline in the study eye, Equivalence was declared if the difference between the 2 treatment groups was within the range [-3.49, +3.49] letters.

Source: CSR QL1205-002 Table 14.2.1.2.1

Table 28. Secondary Estimand - BCVA, Analysis at Week 8 – PP Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
QL1205	284	6.40	0.574	(5.28, 7.53)	(5.46, 7.34)	
Lucentis	284	7.25	0.573	(6.13, 8.38)	(6.31, 8.20)	
QL1205 – Lucentis		-0.85	0.730	(-2.28, 0.58)	(-2.05, 0.35)	0.2421

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; n, number of subjects in the specified category; SE, standard error.

Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm, the stratification factors region (China/India and Europe) and BCVA letters at Baseline (≤66 letters and >66 letters). Dependent variable being the change of BCVA letters from baseline in the study eye, Equivalence was declared if the difference between the 2 treatment groups was within the range [-3.49, +3.49] letters.

Source: CSR QL1205-002 Table 14.2.1.2.2

Table 29. Third Estimand - BCVA, Analysis at Week 8 – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
QL1205	308	6.09	0.561	(4.99, 7.19)	(5.16, 7.01)	
Lucentis	308	7.13	0.562	(6.03, 8.23)	(6.21, 8.06)	
QL1205 – Lucentis		-1.04	0.717	(-2.45, 0.36)	(-2.22, 0.13)	0.1449

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; ITT, Intent-to-Treat population; n, number of subjects in the specified category; SE, standard error.

Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm, the stratification factors region (China/India and Europe) and BCVA letters at Baseline (≤66 letters and >66 letters). Dependent variable being the change of BCVA letters from baseline in the study eye, Equivalence was declared if the difference between the 2 treatment groups was within the range [-3.49, +3.49] letters.

Source: CSR QL1205-002 Table 14.2.1.2.3

Table 30. Third Estimand - BCVA, Analysis at Week 8 - PP Set

Parameter	n	Estimate	SE	95% CI	90% CI	p-value Comparison
QL1205	284	6.40	0.574	(5.28, 7.53)	(5.46, 7.35)	
Lucentis	284	7.25	0.573	(6.13, 8.38)	(6.31, 8.20)	
QL1205 – Lucentis		-0.85	0.730	(-2.28, 0.58)	(-2.05, 0.35)	0.2438

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; n, number of subjects in the specified category; SE, standard error.

Note: Analysis results were produced using multiple imputation. Model included fixed effects for treatment arm, the stratification factors region (China/India and Europe) and BCVA letters at Baseline (≤66 letters and >66 letters). Dependent variable being the change of BCVA letters from baseline in the study eye, Equivalence was declared if the difference between the 2 treatment groups was within the range [-3.49, +3.49] letters.

Source: CSR QL1205-002 Table 14.2.1.2.4

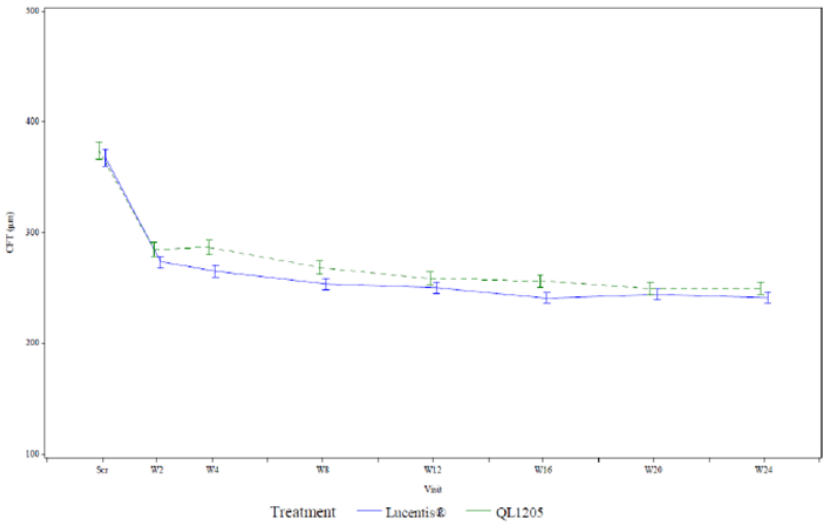
In addition, the applicant presented sensitivity analyses using MMRM (mixed model repeated measures) on the Week 8 results that supported the results from the main analysis of the primary efficacy endpoint.

Secondary endpoint analyses

Several functional and anatomical parameters were assessed as secondary efficacy endpoints, in order to support demonstration of biosimilarity between Rimmyrah and Lucentis.

Change in Central Foveal Thickness (CFT)

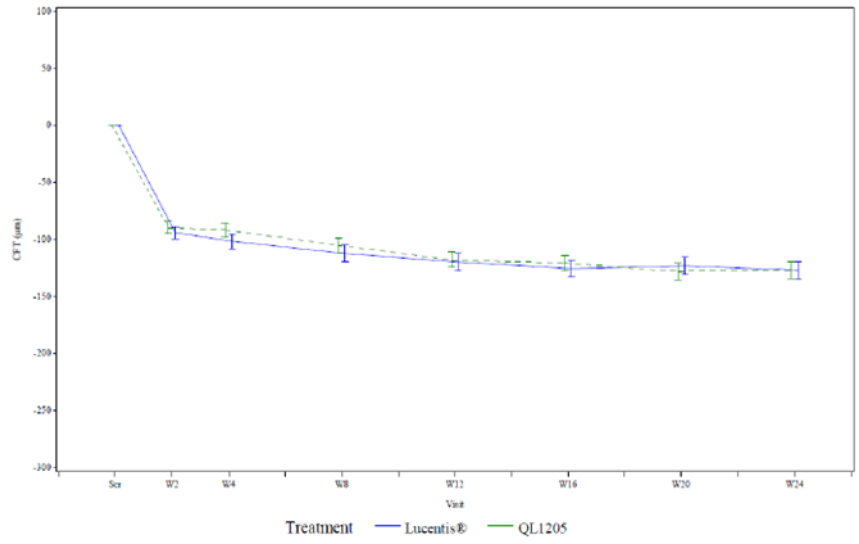
Figure 4. Mean (±SE) Values in CFT by Treatment and Visit – ITT Set



Abbreviations: CFT, central foveal thickness; Scr, Screening; W, Week.

Source: CSR QL1205-002 Figure 14.2.2.3.2

Figure 5. Mean (±SE) Changes from Baseline in CFT by Treatment and Visit – ITT Set



Abbreviations: CFT, central foveal thickness; Scr, Screening; W, Week.

Source: CSR QL1205-002 Figure 14.2.2.3.3

For the change in CFT compared to baseline in the study eye, there was a trend of decrease for both treatment arms, with no statistically significant differences between the groups at Week 4 and Week 8. At Week 4, the mean CFT changes from baseline were -76.4 µm (95% CI -88.9; -63.9) and -87.7 µm (95% CI: -100.2, -75.3) in the Rimmyrah and Lucentis groups, respectively. At Week 8, the mean CFT values were -92.0 (95% CI: -105.3; -78.6) for Rimmyrah and -100.2 (-113.5; -86.6) for Lucentis.

Table 31. Secondary Outcome – Change in Central Foveal Thickness (µm) Mixed Model Repeated Measures – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	Effect	p-value Comparison
Week 2							
QL1205	308	-77.1	5.63	(-88.1, -66.0)	(-86.3, -67.8)		
Lucentis	305	-81.4	5.62	(-92.4, -70.4)	(-90.7, -72.1)		
QL1205 – Lucentis		4.3	7.20	(-9.8, -18.5)	(-7.5, 16.2)		0.5474
Visit							<0.0001
Treatment*visit interaction							0.6619

Parameter	n	Estimate	SE	95% CI	90% CI	Effect	p-value Comparison
Region (China/India and Europe)						14.5	0.0501
BCVA letters at Baseline (≤66 letters and >66 letters)						-42.1	<0.0001
Week 4							
QL1205	308	-76.5	6.36	(-89.0, -64.0)	(-87.0, -66.0)		
Lucentis	305	-87.6	6.35	(-100.1, -75.1)	(-98.1, -77.1)		
QL1205 – Lucentis		11.1	8.33	(-5.3, 27.4)	(-2.7, 24.8)		0.1847
Visit							<0.0001
Treatment*visit interaction							0.6619
Region (China/India and Europe)						14.5	0.0501
BCVA letters at Baseline (≤66 letters and >66 letters)						-42.1	<0.0001
Week 8							
QL1205	308	-91.8	6.79	(-105.2, -78.5)	(-103.0, -80.6)		
Lucentis	305	-100.2	6.80	(-113.5, -86.8)	(-111.4, -89.0)		
QL1205 – Lucentis		8.3	9.00	(-9.3, 26.0)	(-6.5, 23.2)		0.3552
Visit							<0.0001
Treatment*visit interaction							0.6619
Region (China/India and Europe)						14.5	0.0501
BCVA letters at Baseline (≤66 letters and >66 letters)						-42.1	<0.0001
Week 16							
QL1205	308	-105.6	7.20	(-119.7, -91.5)	(-117.5, -93.7)		
Lucentis	305	-109.0	7.21	(-123.1, -94.8)	(-120.9, -97.1)		
QL1205 – Lucentis		3.4	9.61	(15.5, 22.3)	(-12.5, 19.2)		0.7251
Visit							<0.0001
Treatment*visit interaction							0.6619
Region (China/India and Europe)						14.5	0.0501
BCVA letters at Baseline (≤66 letters and >66 letters)						-42.1	<0.0001
Week 24							
QL1205	308	-112.5	7.36	(-127.0, -98.1)	(-124.6, -100.4)		
Lucentis	305	-113.2	7.38	(-127.7, -98.7)	(-125.3, -101.0)		
QL1205 – Lucentis		0.7	9.86	(-18.7, 20.1)	(-15.6, 16.9)		0.9444
Visit							<0.0001
Treatment*visit interaction							0.6619
Region (China/India and Europe)						14.5	0.0501
BCVA letters at Baseline (≤66 letters and >66 letters)						-42.1	<0.0001
Week 52							
QL1205	308	-123.9	7.76	(-139.1, -108.6)	(-136.7, -111.1)		
Lucentis	305	-125.9	7.78	(-141.2, -110.7)	(-138.8, -113.1)		
QL1205 – Lucentis		2.1	10.46	(-18.5, 22.6)	(-15.2, 19.3)		0.8441
Visit							<0.0001

Parameter	n	Estimate	SE	95% CI	90% CI	Effect	p-value Comparison
Treatment*visit interaction							0.6619
Region (China/India and Europe)						14.5	0.0501
BCVA letters at Baseline (≤66 letters and >66 letters)						-42.1	<0.0001

Abbreviations: BCVA, best corrected visual acuity; ITT, Intent-to-Treat; n, number of subjects in the specified category.

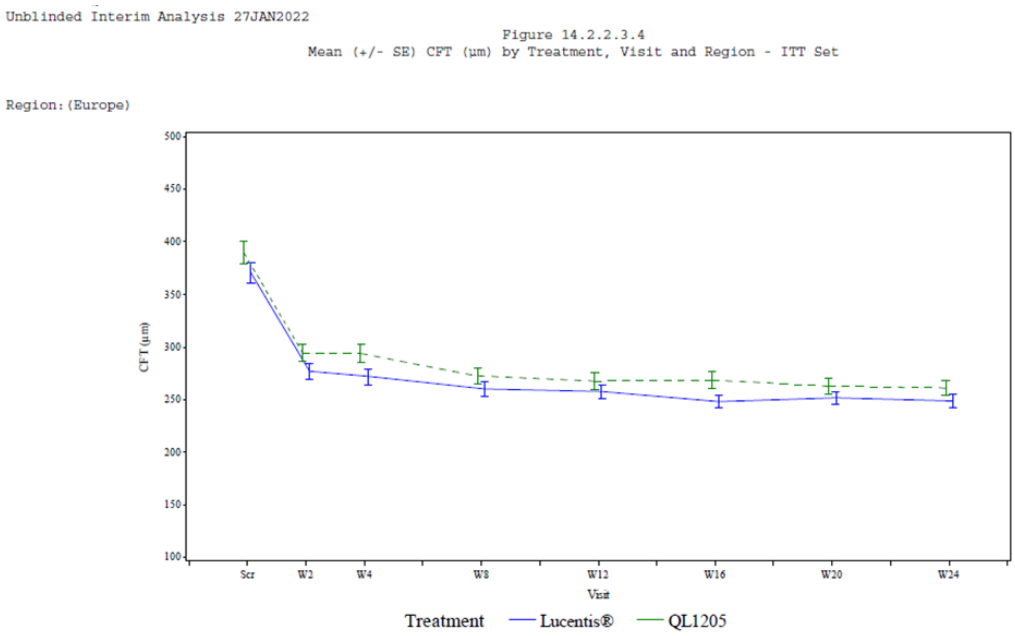
Note: The mixed model repeated measures model included fixed effects of treatment, visit and treatment*visit interaction and the stratification factors region (China/India and Europe) and BCVA letters at Baseline (≤66 letters and >66 letters). Dependent variable was the change in central foveal thickness from baseline in the study eye.

Source: Table 14.2.2.3.6

Clinical improvement with regard to Change in CFT was observed in both study arms, as there was a trend of decrease for both groups up to Week 52, with no statistically significant differences between the groups also at Weeks 2, 16, 24, and 52.

"Region" (China/India versus Europe) was associated with CFT change from baseline to Wk 4 and Wk 8, with higher changes in China/India. However, for the subgroup "Region Europe", the changes from BL in CFT were not meaningfully different between the treatment arms.

Figure 6

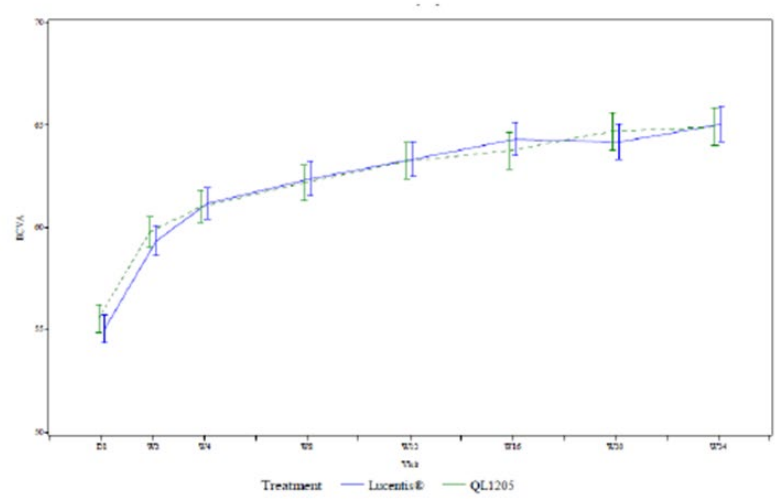


Change in BCVA

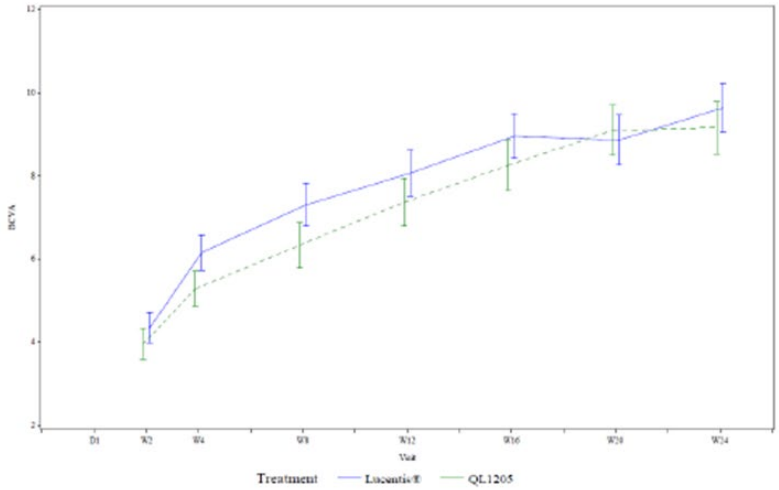
An improvement in BCVA from baseline was observed over time and was comparable between the treatment groups up to Week 24. Generally, visual acuity in terms of BCVA letters using the ETDRS protocol increased over time in both treatment arms with no notable differences observed between the groups.

Figure 7. Mean (±Standard Error) Values and Changes from Baseline in Best Corrected Visual Acuity by Treatment and Visit – Intent-to-Treat Set

Mean Values by Visit



Changes from Baseline



Abbreviations: BCVA, best corrected visual acuity; D, Day; W, Week.
Source: Figure 14.2.1.1.3 and Figure 14.2.1.1.4

Change in Total Size of CNV Leakage Area

The change in total size of CNV leakage area from baseline was evaluated as anatomical EP and was compared between treatment arms at Week 24 and Week 52. Results revealed that the mean change from BL in total size of CNV leakage area in mm^2 was well comparable between the Rimmyrah and Lucentis treatment arms at Wk 24 in the ITT set (QL1205: −0.52 mm^2 [95% CI: -1.11; 0.06], Lucentis: −0.37 mm^2 [-0.96; 0.22]).

Table 32. Secondary Outcome – Total Size of CNV Leakage Area (mm²) at Week 24 Analysis by Visit and Change from Baseline – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	Effect	p-value Comparison
QL1205	234	-0.52	0.298	(-1.11, 0.06)	(-1.01, -0.03)		
Lucentis	226	-0.37	0.302	(-0.96, 0.22)	(-0.87, 0.13)		
QL1205 – Lucentis		-0.15	0.385	(-0.91, 0.60)	(-0.79, 0.48)		0.6911
Region						0.70	0.0812
BCVA letters at Baseline						-0.74	0.0982

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; CNV, choroidal neovascularization; ITT, Intent-to-Treat population; n, number of subjects in the specified category; SE, standard error.
Note: Model included fixed effects for treatment and the stratification factors region (China/India and Europe) and BCVA letters at Baseline. Dependent variable was the change in total size of CNV leakage area from baseline in the study eye.
Source: Table 14.2.2.2.2

Change in Total Size of CNV

The change in total size of CNV compared to baseline at Week 24 was comparable between the treatments (-0.12 mm² [95% CI: -0.42; 0.19] versus -0.20 mm² [-0.51; 0.11] in the Rimmyrah and Lucentis arm, respectively).

Table 33. Secondary Outcome – Total CNV (mm²) at Week 24 Analysis by Visit and Change from Baseline – ITT Set

Parameter	n	Estimate	SE	95% CI	90% CI	Effect	p-value Comparison
QL1205	263	-0.12	0.157	(-0.43, 0.19)	(-0.38, 0.14)		
Lucentis	261	-0.20	0.156	(-0.51, 0.11)	(-0.46, 0.06)		
QL1205 – Lucentis		0.08	0.201	(-0.31, 0.48)	(-0.25, 0.41)		0.6794
Region						0.34	0.1013
BCVA letters at Baseline						-0.32	0.1666

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; CNV, choroidal neovascularization; ITT, Intent-to-Treat population; n, number of subjects in the specified category; SE, standard error.
Note: Model included fixed effects for treatment and the stratification factors region (China/India and Europe) and BCVA letters at Baseline. Dependent variable was the change in total size of CNV leakage area from baseline in the study eye.
Source: Table 14.2.2.2.4

Percentage of Subjects with Loss of ≤ 15 Letters using ETDRS

The percentage of subjects who lost ≤15 letters in BCVA was evaluated at Week 8, Week 24, and Week 52.

For the time points up to Week 24, no notable differences between the treatment arms were observed.

Table 34. Secondary Outcome – Percentage of Subjects wit Loss of ≤15 Letters using ETDRS – ITT Set

Visit	Statistic	QL1205 (N=308)	Lucentis (N=308)	% Difference
Week 2	n	296	299	
	n (%)	295 (99.7)	299 (100.0)	-0.34
	95% *CI*	98.1 - 100.0	98.8 - 100.0	-1.0 - 0.3
Week 4	n	295	298	
	n(%)	295 (100.0)	297 (99.7)	0.34
	95% *CI*	98.8 - 100.0	98.1 - 100.0	-0.3 - 1.0
Week 8	n	283	286	
	n(%)	279 (98.6)	284 (99.3)	-0.71
	95% *CI*	96.4 - 99.6	97.5 - 99.9	-2.4 - 1.0
Week 12	n	281	285	
	n(%)	276 (98.2)	283 (99.3)	-1.08
	95% *CI*	95.9 - 99.4	97.5 - 99.9	-2.9 - 0.7
Week 16	n	284	282	
	n(%)	280 (98.6)	282 (100.0)	-1.41
	95% *CI*	96.4 - 99.6	98.7 - 100.0	-2.8 - -0.0
Week 20	n	274	274	
	n(%)	269 (98.2)	272 (99.3)	-1.09
	95% *CI*	95.8 - 99.4	97.4 - 99.9	-3.0 - 0.8
Week 24	n	275	273	
	n(%)	269 (97.8)	272 (99.6)	-1.82
	95% *CI*	95.3 - 99.2	98.0 - 100.0	**-3.7 - 0.1**

Abbreviations: N = Number of subjects

95% confidence intervals for each treatment are constructed using the Clopper Pearson Method. 95% confidence intervals for the difference was constructed using the Wald Estimate.

Source: CSR QL1205-002 Table 14.2.2.1.1

Percentage of Subjects with Gain of >15 Letters using ETDRS

The proportion of subjects who gained >15 letters in BCVA was evaluated at Week 8, Week 24, and Week 52.

For the time points up to Week 24, no notable differences between the treatment arms were observed.

Table 35. Secondary Outcome – Percentage of Subjects with Gain of >15 Letters using ETDRS – ITT Set

Visit	Statistic	QL1205 (N=308)	Lucentis (N=308)	% Difference
Week 2	n	296	299	
	n(%)	17(5.7)	16(5.4)	0.39
	95% *CI*	3.4 - 9.0	3.1 - 8.5	-3.3 - 4.1
Week 4	n	295	298	
	n(%)	23(7.8)	23(7.7)	0.08
	95% *CI*	5.0 - 11.5	5.0 - 11.4	-4.2 - 4.4
Week 8	n	283	286	
	n(%)	36(12.7)	41(14.3)	-1.61
	95% *CI*	9.1 - 17.2	10.5 - 18.9	-7.2 - 4.0
Week 12	n	281	285	
	n(%)	42(14.9)	50(17.5)	-2.60
	95% *CI*	11.0 - 19.7	13.3 - 22.5	-8.7 - 3.5
Week 16	n	284	282	
	n(%)	53(18.7)	56(19.9)	-1.20
	95% *CI*	14.3 - 23.7	15.4 - 25.0	-7.7 - 5.3
Week 20	n	274	274	
	n(%)	66(24.1)	57(20.8)	3.28
	95% *CI*	19.1 - 29.6	16.2 - 26.1	-3.7 - 10.3
Week 24	n	275	273	
	n(%)	74(26.9)	69(25.3)	1.63
	95% *CI*	21.8 - 32.6	20.2 - 30.9	-5.7 - 9.0

Abbreviations: N = Number of subjects

95% confidence intervals for each treatment are constructed using the Clopper Pearson Method. 95% confidence intervals for the difference was constructed using the Wald Estimate.

Source: CSR QL1205-002 Table 14.2.2.1.2

Changes in Intra- or Sub-retinal Fluid Status

The secondary endpoint 'change in intra- or sub-retinal fluid status' was evaluated by a central reading center over time.

The percentage of subjects with improved status increased in both groups throughout the study, with numerically higher percentages observed in the Rimmyrah group at all time points.

Table 36. Secondary Outcome – Summary of Change in Intra or Sub – Retinal Fluid Status – ITT Set

Visit	Change	QL1205 (N=308)		Lucentis(N=308)	
Week 2	Improved	156	(53.4)	145	(49.2)
	Unchanged	120	(41.1)	124	(42.0)
	Deteriorated	16	(5.5)	26	(8.8)
Week 4	Improved	177	(60.4)	175	(58.9)
	Unchanged	101	(34.5)	104	(35.0)
	Deteriorated	15	(5.1)	18	(6.1)
Week 8	Improved	189	(67.7)	189	(67.5)
	Unchanged	73	(26.2)	70	(25.0)
	Deteriorated	17	(6.1)	21	(7.5)
Week 12	Improved	202	(72.4)	197	(70.1)
	Unchanged	67	(24.0)	68	(24.2)
	Deteriorated	10	(3.6)	16	(5.7)
Week 16	Improved	215	(77.3)	199	(71.3)
	Unchanged	55	(19.8)	62	(22.2)
	Deteriorated	8	(2.9)	18	(6.5)
Week 20	Improved	213	(78.9)	199	(72.6)
	Unchanged	45	(16.7)	60	(21.9)
	Deteriorated	12	(4.4)	15	(5.5)
Week 24	Improved	209	(76.8)	200	(74.1)
	Unchanged	56	(20.6)	54	(20.0)
	Deteriorated	7	(2.6)	16	(5.9)

Abbreviations: ITT, Intent-to-Treat; N, number of subjects.

Source: CSR QL1205-002 Table 14.2.2.3.14

The changes in intra- or subretinal fluid status have been evaluated compared to BL at each visit.

The final data for changes in intra- or subretinal fluid status have been provided with the final updated CSR. Overall, the results reflect an improved status in both treatment arms which increases throughout the study. The percentages of subjects with improved status are comparable between the treatment arms, with no distinct imbalances at the different time points.

Number of Subjects without Intra- or Sub-retinal Fluid

The number of subjects with no intra- or sub-retinal fluid was evaluated in the study eye at Week 24 and at Week 52 and increased in both groups throughout the study until Week 24. No notable differences between the groups were observed.

Table 37. Secondary Outcome – Summary of Subjects without Intra/Sub-Retinal Fluid Status – ITT Set

Visit	Statistic	QL1205 (N=308)	Lucentis(N=308)	% Difference
Screening	n	308	308	
	n(%)	9(2.9)	6(1.9)	0.97
	95% *CI*	1.3 - 5.5	0.7 - 4.2	-1.5 - 3.4
Week 2	n	292	295	
	n(%)	88(30.1)	74(25.1)	5.05
	95% *CI*	24.9 - 35.8	20.2 - 30.4	-2.2 - 12.3
Week 4	n	293	297	
	n(%)	99(33.8)	95(32.0)	1.80
	95% *CI*	28.4 - 39.5	26.7 - 37.6	-5.8 - 9.4
Week 8	n	279	280	
	n(%)	118(42.3)	112(40.0)	2.29
	95% *CI*	36.4 - 48.3	34.2 - 46.0	-5.9 - 10.5
Week 12	n	279	281	
	n(%)	133(47.7)	129(45.9)	1.76
	95% *CI*	41.7 - 53.7	40.0 - 51.9	-6.5 - 10.0
Week 16	n	278	279	
	n(%)	139(50.0)	132(47.3)	2.69
	95% *CI*	44.0 - 56.0	41.3 - 53.4	-5.6 - 11.0
Week 20	n	270	274	
	n(%)	138(51.1)	139(50.7)	0.38
	95% *CI*	45.0 - 57.2	44.6 - 56.8	-8.0 - 8.8
Week 24	n	272	270	
	n(%)	142 (52.2)	136 (50.4)	1.84
	95% *CI*	46.1 - 58.3	44.2 - 56.5	-6.6 - 10.3

N = Number of subjects

95% confidence intervals for each treatment are constructed using the Clopper Pearson Method. 95% confidence intervals for the difference was constructed using the Wald Estimate.

Source: CSR QL1205-002 Table 14.2.2.3.15

Subjects with Retinal Pigment Epithelium Detachments

The number of subjects with RPE detachments decreased from baseline to Week 24 in both treatment arms, with no notable differences between the treatment arms.

Table 38. Secondary Outcome – Summary of Subjects with Retinal Pigment Epithelium Detachments – ITT Set

Visit	Statistic	QL1205 (N=308)	Lucentis (N=308)	% Difference
Screening	n	308	308	
	n (%)	39 (12.7)	45 (14.6)	-1.95
	95% CI	9.2 – 16.9	10.9 – 19.1	-7.4 – 3.5
Week 24	n	266	264	
	n (%)	21 (7.9)	26 (9.8)	-1.95
	95% CI	5.0 – 11.8	6.5 – 14.1	-6.8 – 2.9

Abbreviations: CI, confidence interval; ITT, Intent-to-Treat population; N, number of subjects; n, number of subjects at the specified time point.

Note: 95% CIs for each treatment were constructed using the Clopper-Pearson Method. 95% CIs for the difference was constructed using the Wald Estimate.

Source: CSR QL1205-002 Table 14.2.2.2.5

Overall, comparability of Rimmyrah to Lucentis was demonstrated for all secondary efficacy endpoints up to Week 24. Results were consistent over time for all variables (up to Wk 24). Improvement of macular function in terms of BCVA demonstrated after Week 8 was maintained until the end of the observation period.

Graphical presentations of efficacy outcomes are provided with Mean±SE. In general these figures are endorsed, but the standard error is not considered a suitable measure of variability in these figures, as it does not convey full information about the distribution of the mean (i.e. t-distribution). During the procedure, the relevant figures for efficacy outcomes have been provided with mean ± SD, as requested. No notable differences between treatment arms with regard to variability are observed.

Ancillary analyses

Various supportive analyses were performed for the primary EP: analysis without imputation, within strata analysis, tipping point analysis, analyses by BL BCVA letters and by region.

The results of the ancillary analyses for the primary EP were overall supportive for the primary analysis.

With regard to the 'within strata' analysis, the point estimates for all strata were within the equivalence margin of ± 3.49 letters. However, the within strata supportive analyses of ITT and PP set have shown a significant effect of region. The additional analysis by region has shown that 95% CI for some regions (China, India) also fall outside of the equivalence margin. The applicant explains the lack of consistency in the primary efficacy endpoint among various regions with a small sample size. The applicant further claims that the absolute value of estimate of difference does not cross the pre-defined equivalence margin. This can be considered acceptable.

A tipping point analysis was conducted to assess robustness of results for the primary estimand. The base dataset was the primary estimand with the non-monotone MAR imputation, composite strategy and MNAR imputation implemented; the tipping point assesses the effects of delta shift on the monotone MAR imputation employed for the primary estimand (results not presented).

2.4.7. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical similarity comparison was based on one single pivotal Phase 3 trial. The **QL1205-002 Phase 3 study** in subjects with nAMD was designed to demonstrate similarity with regard to efficacy between Rimmyrah and EU-Lucentis. An additional Phase 1 study, QL1205-001, was conducted in Chinese patients with nAMD in order to evaluate the preliminary safety of Rimmyrah, upon request of the Chinese NCA (CDE).

It is acceptable that no further clinical studies have been conducted to demonstrate efficacy similarity between Rimmyrah and EU-Lucentis in other adult indications approved for EU-Lucentis. The selected patient population is considered a relevant and sensitive study population for the detection of potential differences between Rimmyrah and the reference product and was endorsed by the EMA. It is endorsed that EU-Lucentis was chosen as comparator.

Overall, the applicant's development program to demonstrate similarity between Rimmyrah and EU-Lucentis with respect to efficacy is considered adequate to support this application: study design, study population, inclusion/exclusion criteria, and dose regimen were performed in line with the guidance on similar biological products and were overall in compliance with scientific advice obtained from the EMA.

In the pivotal Phase 3 study QL1205-002, 616 patients from 97 study sites were randomized 1:1 to receive either Rimmyrah or EU-Lucentis (n=308 in each treatment arm). Randomization was stratified by geographic region (China/India vs. Europe) and the BCVA letters at Baseline (≤ 66 letters vs. > 66 letters). The study was conducted globally in 11 countries with 7 EU member states. Overall 367 patients from the region "Europe" were enrolled (n=184 in the Rimmyrah arm, n=183 in the Lucentis arm). The applicant confirms that this study was performed in compliance with ICH guidelines on GCP as well as the ethical principles of the latest revision of the Declaration of Helsinki. The study itself was not inspected by an EU NCA. However, study sites in India were subject to EMA inspections, sites in China were inspected by the NMPA, Hungarian sites by local authorities and by the PMDA, and Latvian and Slovakian sites by local authorities. No issues regarding GCP have been identified.

Demographics and baseline disease characteristics including the concomitant/prior medication and ophthalmological medical history were representative for the nAMD population and were overall comparable between the treatment arms. There was a higher proportion of patients with ocular surgery in the Lucentis group compared to Rimmyrah group (40.3% vs 32.8%). The majority of the ocular surgeries were cataract operations. In detail, more patients in the Lucentis group underwent the cataract operation (37.3%) in comparison to the Rimmyrah group (29.5%). The applicant notes that these ocular surgeries were allowed to be performed up to 3 months prior to randomization. It has to be noted that even if a higher proportion of patients underwent a cataract surgery in the Lucentis group, the patients were randomized according to the BCVA, hence this disproportion could not have impacted the results.

The mean duration (in weeks) since first diagnosis was longer in the Lucentis group than in the Rimmyrah group (12.3 ± 47.26 weeks vs. 9.5 ± 21.93 weeks). This imbalance was attributed to the presence of outliers with long duration of disease, which was more present in the Lucentis than in the Rimmyrah arm. In the Lucentis arm, there were 2 patients included with more than 500 weeks from first diagnosis to study BL. This explanation is considered reasonable.

Eligible randomized patients received either Rimmyrah or EU-Lucentis on Day 1 every 4 weeks into the study eye. Treatment was repeated up to Week 48 for a total of 13 doses of study drug. Study duration was 52 weeks.

Unmasked personnel was administering the study treatments to patients. This could have introduced a bias to the study. The applicant clarified that the site personnel had no overlap between the masked and unmasked task delegations and the unmasked personnel did not have access to case report forms. This is acceptable.

With dossier submission, the Week 24 data set has been submitted with an interim clinical study report. For this interim CSR, data cut-off was 27 January 2022. For further substantiation of the similarity between Rimmyrah and EU-Lucentis, the final 52 weeks data were submitted during the MAA procedure.

Overall, the design of the pivotal Phase 3 study is considered adequate and generally in line with previous EMA-scientific advices. The inclusion and exclusion criteria were in line with those in the clinical trials performed with Lucentis and are overall considered adequate. A lower BCVA boundary of 20/100 at baseline was recommended for study inclusion by the CHMP during prior SA (instead of 20/200, as defined by the applicant in the inclusion criteria), in order to obtain a more homogenous group allowing for evaluation of potential more pronounced loss of vision. This was not followed by the applicant. Against this background, the applicant was requested to provide a subgroup analysis for the primary EP for the subgroup of patients with a baseline BCVA between 20/40 and 20/100, also by region. The analysis showed that the mean change in BCVA (letters) at Wk 8 in the subgroup of patients with a BL BCVA between 20/40 and 20/100 was 5.84 (95% CI: 4.51, 7.18) in the Rimmyrah arm and 6.23 in the Lucentis arm (95% CI: 4.80, 7.66) (ITT population). Biosimilary could be concluded, since the 95% CI of the adjusted treatment difference of -0.39 letters was [-2.15; 1.37], which was completed contained in the pre-specified margin of ±3.49 letters. In the PP population, the mean change in BCVA (letters) at Wk 8 in this subgroup was 6.08 (95% CI: 4.69, 7.48) in the biosimilar arm and 6.14 (95% CI: 4.65, 7.63) in the originator arm, with an adjusted treatment difference of -0.06 letters [95% CI: -1.89; 1.78]. The same picture was observed in this subgroup when analysed by region, with similar mean changes in BCVA (letters) for Rimmyrah compared to Lucentis (region Europe: 5.94 vs 6.44 letters BCVA change).

The applied treatment regimens for ranibizumab (0.5 mg IVT injection every 4 weeks) were in line with the Lucentis labelling. The most common reasons for premature discontinuation until DCO were consent withdrawal, adverse events and "other reasons". Until DCO, n=17 (5.5%) in the Rimmyrah arm and n=27 (8.8%) in the Lucentis arm discontinued the study prematurely. 3 patients in the Rimmyrah arm and 7 patients in the EU-Lucentis arm discontinued the study prematurely due to "other reasons" until DCO. The applicant clarified the "other" reasons leading to premature study discontinuation until DCO for IA. Those reasons were mainly the COVD-19 pandemic, death, refusal to visit or to continue, as well as "personal" reasons. Furthermore, an updated subject disposition table has been provided with the final updated CSR, with all randomized participants included (final data set). Here, an exhaustive list of the reasons for premature study discontinuation is included. No notable differences or imbalances between the treatment arms were noted.

The percentage of protocol deviations was comparable between the Rimmyrah and Lucentis group.

The focus of a clinical comparability trial is to demonstrate similar efficacy and safety compared to the reference product. Comparability margins have to be pre-specified and justified based on clinical relevance. Adequate data on the effect size should be considered to support the selection of the margin. The biosimilarity margin for the main efficacy endpoint needs to be justified on both clinical and statistical grounds, in order to ensure that there are no clinically relevant differences in efficacy and to prove that there is no important loss of efficacy if the test product is used instead of reference.

With regard to demonstration of similar efficacy between Rimmyrah and EU-Lucentis, an equivalence margin of ± 3.49 letters was chosen. However, this margin was implemented rather late (i.e. with a protocol amendment [protocol version 4 dated 04 Jun 2021], where the margin was widened from ±

3.0 to ± 3.49 letters). In addition, with this amendment the sample size was reduced from approximately 656 to at least 580 subjects to be enrolled and randomized. At the time of writing the amendment, this sample size was already enrolled. With his responses to the D120 LoQ, the applicant assured that changes to the study design were made without knowledge of the primary outcome and that the respective study personnel was blinded.

The applicant was requested to justify the protocol amendment that introduced equivalence margin change from [-3.0, +3.0] to [-3.49, +3.49]). Although in line with the Scientific advice from 2021, this amendment was done while the study was already ongoing and therefore could have introduced a bias. The applicant should specifically comment on the reasons for the change. Furthermore, data on how many patients have passed the time point for the evaluation of primary efficacy endpoint at the time of the margin amendment were expected.

The applicant has shown that at the time of protocol amendment that had introduced a change in equivalence margin from [-3.0, +3.0] to [-3.49, +3.49], 93% of patients had reached the time for primary endpoint measurement (8 weeks). Hypothetically, as this change of equivalence margin was done after a majority of patients have passed the time for primary endpoint evaluation, this amendment could have been data driven. However, as the primary efficacy endpoint fits also in the former equivalence margin [-2.46, 0.36], such data driven change is not assumed.

A clinical justification for the margin was not presented, and CHMP recommended a margin below ±3.5 in Scientific Advice. However, since in preceding ranibizumab biosimilar approval procedures, equivalence margins of ± 3.5 letters have been accepted, the chosen margin can overall be agreed.

In the **supportive study QL1205-001**, only exploratory efficacy analyses were performed in 48 Chinese nAMD patients with a BCVA of 20/32 to 20/400 who received overall 3 doses of either 0.5 mg Rimmyrah or Lucentis. Therefore, the focus of the efficacy assessment lies on the data from the pivotal Phase 3 comparative efficacy study QL1205-002 that have been submitted for demonstration of therapeutic equivalence between Rimmyrah and EU-Lucentis.

From the efficacy data presented in the final CSR, there were no indications for relevant differences between Rimmyrah and Lucentis regarding functional and anatomical efficacy parameters in the population studied. The change in BCVA as exploratory efficacy endpoint was comparable between Rimmyrah and Lucentis.

Efficacy endpoints

The primary endpoint in the pivotal Phase 3 comparative efficacy study was the 'Change from baseline in BCVA letters [ETDRS] at Week 8' in the ITT population. The Per Protocol population was used as a supportive population by the applicant for evaluation of the sensitivity of the primary efficacy analysis, but from a regulatory perspective in an equivalence setting, the PP set is equally important, and similarity has to be shown in both analysis sets (see ICH E9).

The proposed primary EP is a validated and sensitive functional endpoint and was agreed on by CHMP during the prior SA procedure.

The secondary efficacy endpoints include change in CFT compared to BL at different time points (Wk 2, 4, 8, 16, 24 and 52), BCVA change from BL over time, change in total size of CNV leakage area as well as total size of CNV at Wk 24 and 52 compared to BL, as well as percentage of subjects with loss of ≤15 letters and with gain of >15 letters from BL at Wk 8, 24, and 52. In addition, changes in intra- or subretinal fluid status, number of subjects without intra- or subretinal fluid at Wk 24 and 52, and number of subjects with RPE detachments were explored as secondary endpoints.

For the secondary endpoint 'change in intra- or sub-retinal fluid status', the applicant has clarified that the changes in intra- or subretinal fluid status have been evaluated compared to BL at each visit. The

final data for changes in intra- or subretinal fluid status have been provided with the final updated CSR. Overall, the results reflect an improved status in both treatment arms which increases throughout the study. The percentages of subjects with improved status are comparable between the treatment arms, with no distinct imbalances at the different time points.

Efficacy data and additional analyses

For the primary endpoint 'Change from Baseline in BCVA letters at Week 8' in the ITT population, a mean change from baseline of 6.08 ETDRS letters (95% CI: 4.98; 7.18) was observed for Rimmyrah, compared to 7.13 letters (95% CI: 6.03; 8.23) for EU-Lucentis.

Equivalence was concluded, since the 95% CI of the adjusted treatment difference of -1.05 ETDRS letters was [-2.46; 0.36], which was completely contained within the predefined equivalence margin of ±3.49 letters. Thus, formal similarity of efficacy with regard to the primary efficacy endpoint was demonstrated.

This was supported by sensitivity analyses: Similar mean differences were also observed in the PP population, with 95% CIs within the predefined equivalence margin.

Strategies to deal with intercurrent events were defined in the statistical analysis plan only. The main estimand includes a complex approach (composite "return to baseline" strategy for death and discontinuation of study treatment due to AE, LoE or need for rescue medication, and hypothetical "imputing based on subjects not experiencing the intercurrent event" strategy for discontinuations for reasons other than AE, LoE or need for rescue medication).

Since the strategy was not defined in the study protocol, results across different strategies are required to consistently show equivalence of the treatment effect.

The applicant provided information on the incidence of those intercurrent events that were specified in the study protocol. It is agreed that the incidence is small and that there are no strong imbalances. This provides reassurance.

The applicant also provided sensitivity analyses as requested. In short, results are reassuring. The tipping-point analyses suggest that in the ITT set a tipping-point for equivalence (i.e. tipping-point at which the 95% CI is no longer included in ±3.49) in the imputation of missing values on top of a simple treatment policy analysis lies somewhere around a ≥12 point difference in favour of Lucentis or a ≥40 point difference in favour of Rimmyrah, this is observed across several scenarios. In the PP set the tipping-points are further away from no difference. In light of the observed change from baseline in BCVA in either treatment group, these scenarios appear highly unlikely. Thus, the tipping-point analyses provide good reassurance that results are robust.

Several functional and anatomical parameters were assessed as secondary efficacy endpoints, in order to support demonstration of biosimilarity between Rimmyrah and EU-Lucentis.

For the change in CFT compared to baseline in the study eye, there was an initial trend for a CFT decrease for both treatment arms followed by a plateau from Wk 2 on. At Week 4, the mean CFT changes from baseline were -76.4 µm (95% CI -88.9; -63.9) and -87.7 µm (95% CI: -100.2, -75.3) in the Rimmyrah and Lucentis arms, respectively. At Week 8, the mean CFT changes from BL were -92.0 (95% CI: -105.3; -78.6) for Rimmyrah and -100.2 (-113.5; -86.6) for Lucentis.

There were no statistically significant differences observed for CFT at Wk 4 and at Wk 8 between the treatment groups. The pending data for the time points Wks 2, 16, 24, and 52 have been presented with the responses to the D120 LoQ and support similar efficacy between QL120 and Lucentis.

There was an effect observed for the factor "Region" (China/India versus Europe) for the change in CFT compared to BL. However, for the subgroup "Region Europe", the changes from BL in CFT were not significantly different between the treatment arms.

An improvement in BCVA from baseline was observed over time and was comparable between the treatment groups up to Week 24. Generally, visual acuity in terms of BCVA letters using the ETDRS protocol increased over time in both treatment arms with no notable differences observed between the groups.

The anatomical EP change in total size of CNV leakage area from baseline was compared between the treatment arms at Week 24 and Week 52. Results revealed that the mean change from BL in total size of CNV leakage area in mm^2 was well comparable between the Rimmyrah and Lucentis treatment arms at Wk 24 in the ITT set (QL1205: −0.52 mm^2 [95% CI: -1.11; 0.06], Lucentis: −0.37 mm^2 [-0.96; 0.22]).

The change in total size of CNV compared to baseline at Week 24 was comparable between the treatments (-0.12 mm^2 [95% CI: -0.42; 0.19] versus -0.20 mm^2 [-0.51; 0.11] in the Rimmyrah and Lucentis arm, respectively). The data for Wk 52 still need to be provided.

The percentage of subjects who lost ≤15 letters in BCVA was comparable between the 2 treatment arms at all visits (approximately ≥98%).

The proportion of subjects who gained >15 letters in BCVA was also comparable between the 2 treatment groups throughout the study.

For the secondary endpoint 'change in intra- or sub-retinal fluid status', the changes in intra- or subretinal fluid status have been evaluated compared to BL at each visit. The final data for changes in intra- or subretinal fluid status have been provided with the final updated CSR. Overall, the results reflect an improved status in both treatment arms which increases throughout the study. The percentages of subjects with improved status are comparable between the treatment arms, with no distinct imbalances at the different time points.

The number of subjects with no intra- or sub-retinal fluid increased in both groups throughout the study until Week 24. No notable differences between the groups were observed.

The number of subjects with RPE detachments decreased from baseline to Week 24 in both treatment arms, with no notable differences between the treatment arms.

Overall, comparability of Rimmyrah to Lucentis was demonstrated for all secondary efficacy endpoints up to Week 24. Results were consistent over time for all variables (up to Wk 24). Improvement of macular function in terms of BCVA demonstrated after Week 8 was maintained until the end of the observation period.

During the procedure, the applicant has provided updated analyses for all secondary efficacy endpoints, including Week 52 data. Outcomes for the secondary endpoints remained the same: no notable differences were detected between the treatment arms with regard to efficacy similarity.

Various supportive analyses were performed for the primary EP, including an analysis without imputation of missing values, within strata analysis, tipping point analysis, analyses by BL BCVA letters and by region.

The results of the ancillary analyses for the primary EP were overall supportive for the primary analysis.

With regard to the 'within strata' analysis, the point estimates for all strata were within the equivalence margin of ± 3.49 letters. However, the within strata supportive analyses of ITT and PP set have shown

a significant effect of region. The additional analysis by region has shown that 95% CI for some regions (China, India) also fall outside of the equivalence margin. The applicant explains the lack of consistency in the primary efficacy endpoint among various regions with a small sample size. The applicant further claims that the absolute value of estimate of difference does not cross the pre-defined equivalence margin. This can be considered acceptable.

2.4.8. Conclusions on the clinical efficacy

The clinical efficacy data shows similarity with regard to efficacy between Rimmyrah and the EU reference product.

2.4.9. Clinical safety

Two clinical studies were conducted to compare the safety profiles of Rimmyrah and Lucentis:

A multicentre **pivotal Phase 3 study (QL1205-002)** was conducted in Europe, China and India and including a total of 616 subjects diagnosed with nAMD who received 0.5mg ranibizumab (either Rimmyrah or EU-Lucentis) by IVT injection once every 4 weeks with 13 consecutive doses. In addition, a **supportive Phase 1 study (QL1205-001)** was conducted in China including 48 AMD patients who received either Rimmyrah or Lucentis once every 4 weeks for 3 consecutive doses.

Table 39. Overview of the Clinical Development Plan for Evaluation of Safety Comparability

Study	Study Objectives	Design	Study Population	Safety Endpoints
QL1205-001 Phase 1 (China) wAMD subjects	Primary objective: To conduct preliminary evaluation on the clinical safety after intravitreal injection of QL1205 or Lucentis in patients with wAMD. Secondary objective: To conduct preliminary evaluation on the clinical efficacy and PK characteristics after intravitreal injection of QL1205 or Lucentis in patients with wAMD.	Randomised, double-blind, parallel, positive (Lucentis) -controlled study; Intravitreal injection 0.5 mg (0.05 mL) once every 4 weeks for 3 consecutive doses, either QL1205 or Lucentis Total duration: 12 weeks	48 Chinese wAMD subjects (23 for QL1205, 25 for Lucentis)	· Incidence of AEs and SAEs · Abnormalities in clinical laboratory examination · Abnormalities in physical examination · Abnormalities in 12-lead electrocardiogram (ECG) · Abnormalities in abdominal ultrasound scan · Abnormalities in chest X-ray · Abnormalities in intraocular pressure
QL1205-002 Phase 3 (EU, China/India) wAMD subjects	Primary objective: To demonstrate that the biosimilar candidate QL1205 is equivalent to Lucentis (ranibizumab) in subjects with wAMD. Secondary objective · To evaluate the efficacy of QL1205 versus Lucentis in subjects with wAMD based on central foveal thickness (CFT), area of CNV, and leakage from CNV lesion. · To evaluate the systemic exposure of QL1205 versus Lucentis in subjects participating in PK evaluation. · To evaluate the safety or QL1205 versus Lucentis. · To evaluate immunogenicity of QL1205 versus Lucentis	Randomised, double-masked, parallel-group, multiregional, multicentre study; IVT injection 0.5 mg (0.05 mL) once every 4 weeks for 13 consecutive doses, either QL1205 or Lucentis Total duration:52 weeks	616 wAMD subjects (308 for QL1205, 308 for Lucentis)	· Adverse events, as defined by treatment-emergent AEs (TEAEs), SAEs, related TEAEs and related SAEs · Injection site reactions · Intraocular inflammation · Laboratory parameters (hematology, clinical chemistry, urinalysis, vital signs, etc) · Intraocular pressure and perfusion of the optic nerve · Ophthalmological examinations · FA, OCT, IOP, slit-lamp examination, and dilated fundus examination

[Table 39: Table 2.7.4-1 from Summary of Clinical Safety]

Key safety information was derived from the Phase 3 study QL1205-002, supported by safety and tolerability data from the Phase 1 study.

Posology

The dose and route of administration for Rimmyrah will be identical to that of the approved Lucentis. The recommended dose for Lucentis is 0.5 mg (0.05 mL) given as a single intravitreal (IVT) injection once a month. In patients with wAMD, DME and RVO initially three or more consecutive, monthly injections may be needed.

Rimmyrah will be presented as a vial only or as a vial plus filter needle pack, to be administered by a qualified ophthalmologist experienced in IVT injections. The sterile syringe plus injection needle required for adult patients will not be included in the presentation.

The applicant seeks approval for both presentations in one marketing authorisation application (MAA) procedure.

The Q4W administration of the study drugs is in agreement with the anticipated posology in patients with the highest treatment need. From a safety perspective, a monthly schedule is most sensitive, as higher exposure levels can be expected in comparison with a treat and extend regimen, and is thus supported.

Study duration of the pivotal Phase 3 study was 12 months, with 13 monthly injections. A study duration of 12 months is considered a relevant time period to assess safety and immunogenicity in a biosimilarity exercise.

With dossier submission, only safety data until DCO were submitted with an interim CSR. The final 52 weeks safety data have been submitted during the MAA procedure and confirmed comparable profile with the known profile of the reference medicinal product.

Indications

Lucentis was initially authorized in 2007 in the EU/EEA for the treatment of nAMD. Later on, the following indications were granted: treatment of visual impairment due to DME, RVO and CNV, treatment of PDR, and treatment of ROP.

Originally, the applicant claimed the same therapeutic indications for Rimmyrah as granted for Lucentis in the EU, including the ROP indication in preterm infants. This was not considered acceptable, since no suitable device for administration to the paediatric population has been presented by the applicant However, during the MA procedure, the applicant decided to withdraw the claim for the ROP indication, as a response to the D120 LoQ. Thus, only the Lucentis-approved adult indications are applied for.

Neovascular AMD is considered a sufficiently sensitive population to investigate clinical biosimilarity in terms of safety, as there is comparability for ranibizumab across indications with regard to target receptor, mode of action and safety across authorised indications, i.e., DME, RVO, CNV and PDR. In addition, immunogenicity of ranibizumab was reported to be overall low across indications (up to 9%).

Safety profile of the reference product

The majority of AEs reported following administration of Lucentis are related to the intravitreal injection procedure. The most frequently reported ocular adverse reactions following injection of Lucentis are: eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus. The most frequently reported non-ocular adverse reactions are headache, nasopharyngitis and arthralgia. Less frequently reported, but more serious, adverse reactions include endophthalmitis, blindness, retinal detachment, retinal tear and iatrogenic traumatic cataract (refer to the Lucentis SmPC).

Class effects known to be observed with systemic VEGF inhibition are hypertension, arterial thromboembolism, cardiac ischemia, haemorrhages, proteinuria/nephrotic syndrome, delayed wound healing and intestinal perforation.

IVT injections, including those with ranibizumab, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis. Sustained IOP increases have also been identified [Lucentis SmPC, Section 4.8 and RMP].

As with all therapeutic proteins, there is potential for an immune response in patients treated with Lucentis. Intraocular inflammations that increase in severity may be a clinical sign attributable to intraocular antibody formation.

In the pivotal Phase 3 study, safety was assessed based on the occurrence of adverse events (AEs) and serious adverse events (SAE) categorised by SOC and PT and coded by MedDRA as well as any changes in vital signs, laboratory assessment, and immunogenicity. The Safety Set (SAF) in each study included any individuals who received at least one or more dose of IMP.

Per treatment arm, 309 (QL1205) and 307 (EU-Lucentis) patients were included in the SAF of the pivotal Phase 3 study, respectively. This was due to the fact that one subject was administered an incorrect IMP kit at Day 1 visit because of site error (i.e. randomized to Lucentis but received QL1205). This subject was subsequently discontinued from study treatment because of an SAE of stroke and did not receive any more doses (i.e. only received 1 dose of QL1205).

In general, to characterize the ADR pattern over time, the cohort of exposed subjects should be large enough to observe also less frequently occurring events. To detect a common AE (appearing in ≥1% of patients) with sufficient precision, at least 300 subjects need to be treated. Further, as per ICH E1, 100 patients exposed to a study drug for a minimum of one year is considered acceptable, and 300-600 patients should be treated for 6 months with the drug at the intended dose level. Thus, the data base of more than 300 subjects per treatment arm in the pivotal Phase 3 study is considered acceptable.

During the Pre-Submission meeting for Rimmyrah, it was agreed that the safety data from the two studies QL1205-001 and QL1205-002 will be presented separately in the MAA dossier because of differences in study design, the number of IMP administrations in each study, and eligibility criteria of the enrolled population in each of the studies.

2.4.9.1. Patient exposure

Pivotal Phase 3 study QL1205-002

Comparative safety data from the pivotal Phase 3 study involved 616 randomized patients (QL1205: n=309, EU-Lucentis n=307), most of whom (n=596, 96.4%) completed the study treatment up to Week 24.

The number of patients per treatment arm treated for one year complies with the ICH E1 guideline (usually comparative date from at least 100 patients exposed for a minimum of one-year would be expected) and are acceptable.

The mean (SD) age, weight, and height for all subjects were 71.4 (9.14) years, 72.07 (14.294) kg, and 164.16 (9.456) cm, respectively. Overall, the proportions of male and female subjects were generally balanced (304 males, 49.4%; 312 females, 50.6%). The majority of subjects was above the

age of 70 years (336 subjects, 54.5%). With regard to race, most subjects were White (366 subjects, 59.4%) or Asian (249 subjects, 40.4%).

Baseline disease characteristics with regard to BCVA, CFT, and CNV have been presented by the applicant and are overall comparable between the treatment arms.

Overall, a comparable number of patients in the Rimmyrah (80.5%) and Lucentis (84.7%) treatment arms had an ophthalmologic history in the study eye ongoing at screening.

The number of patients in the Rimmyrah and Lucentis treatment arms who had a non-ophthalmic medical history was comparable (264 [85.7%] patients in Rimmyrah and 266 [86.4%] patients in the Lucentis treatment arms), with medical history reported most frequently in the SOC Vascular disorders, PT Hypertension (n=191 [62.0%] versus n=183 [59.4%]).

Prior medications were used only by few study participants (QL1205: n=31 [10.0%], Lucentis: n=21 [6.8%]). As prior medications, predominantly ophthalmologics were used.

Overall, the use of concomitant medications was reported for most patients of the SAF (QL1205: n=285, Lucentis: n=279). Concomitant medications included predominantly antithrombotic agents, lipid-modifying agents and thyroid therapies. The most frequently used concomitant medications in the study eye were antiinfectives. The use of concomitant medications was overall balanced between treatment arms.

For further details on demographic and baseline characteristics, please refer to Overview Section 3.3.4.2 'Baseline data'. Overall, baseline characteristics were balanced between treatment arms, and the population that was investigated was sufficiently sensitive for the evaluation of similarity from a safety (and efficacy) perspective.

A total of 919 subjects were screened, of whom 616 subjects were randomised 1:1 into either the Rimmyrah treatment group or the EU Lucentis treatment group (308 in the Rimmyrah treatment group and 308 in the EU Lucentis treatment group in ITT set).

All 616 randomized subjects were included in the Safety Set (309 in the Rimmyrah treatment group and 307 in the Lucentis treatment group in safety set). One subject randomized to Lucentis was included under the Rimmyrah group in the Safety Set (Listing 16.2.2.1): Subject was administered an incorrect investigational medicinal product kit at Day 1 visit because of site error (ie, randomized to Lucentis but received QL1205); the subject was subsequently discontinued from study treatment because of an SAE of stroke and did not receive any more doses (ie, only received 1 dose that was QL1205) (Listing 16.2.5.1).

Of the 616 randomised subjects, 594 subjects (96.4%) completed the study treatment up to Week 24 while 22 subjects (3.6%) did not (n=10 in the Rimmyrah arm, n=12 in the Lucentis arm). The main reason for not completing the study treatment up to Week 24 was subject withdrawal of consent (9 subjects, 1.5%), followed by AE and other reasons (5 subjects each, 0.8%). Of the 616 randomised subjects, 44 subjects (7.1%) discontinued the study prematurely as of the data cut-off of 27 Jan 2022 (n=17 in the Rimmyrah arm, n=27 in the Lucentis arm), mainly because of withdrawal of consent (18 subjects, 2.9%), followed by AE and other reasons (10 subjects each, 1.6%).

Please refer to Overview Section 3.3.4.2 'Participant flow' for details.

Treatment compliance up to Week 8 was 97.4% in the Rimmyrah group and 98.5% in the Lucentis group. Compliance up to Week 24 was 99.01% in the Rimmyrah group and 99.27% in the Lucentis group. There were no notable differences in treatment compliance between the 2 groups.

Table 40. Treatment Compliance – Safety Set

	QL1205 (N=309)	Lucentis (N=307)
Compliance up to Week 8		
n	309	307
Mean (SD)	97.4 (11.10)	98.5 (8.45)
Median	100.0	100.0
Min, Max	50, 100	50, 100
Compliance up to Week 24		
n	309	307
Mean (SD)	99.01 (5.849)	99.27 (3.943)
Median	100.00	100.00
Min, Max	42.9, 100.0	60.0, 100.0

Abbreviations: Max, Maximum; Min, Minimum; N, number of subjects; n, number of subjects in the specified category; SD, standard deviation
Note: Compliance up to Week 8 = (number of actual doses administered/number of planned doses)*100%, up to and including Week 4.
Compliance up to Week 24 = (number of actual doses administered/number of planned doses)*100%, up to and including Week 24.
Source: Table 14.1.5.1

[Table 40: Table 10 from Interim CSR]

Subjects were randomised to receive either Rimmyrah or EU Lucentis 0.5 mg (0.05 mL) once every 4 weeks with 13 consecutive injections up to Week 48 for the randomised, double-masked, parallel-group period. As there were a large number of subjects who had completed the study as of the cut-off date of 27 Jan 2022, the extent of exposure was long with a mean (SD) duration of exposure of 311.5 (64.55) days for Rimmyrah and 305.8 (71.78) days for Lucentis. The exposure to Rimmyrah was slightly longer with a maximum of 356 days compared to 348 days in the Lucentis arm.

Table 41. Exposure to Study Treatment - SS

	QL1205(N=309)	Lucentis(N=307)
Duration of exposure (days)		
n	309	307
Mean (SD)	311.5 (64.55)	305.8 (71.78)
Median	337.0	337.0
Min, Max	1, 356	1, 348

Abbreviations: Max, Maximum; Min, Minimum; N, number of subjects; n, number of subjects in the specified category; SD, standard deviation
Source: CSR Phase 3 QL1205-002 Table 14.3.4.4

Data on the mean cumulative amount (mg) of study drug administered up to Week 24 as well as up to Week 52 by treatment arm were presented, as requested.

Table 42. Exposure to Study Treatment – Safety Set

	QL1205 (N=309)	Lucentis (N=307)
Duration of exposure (days)		
n	309	307
Mean (SD)	317.6 (63.03)	313.5 (70.39)
Median	337.0	337.0
Min, Max	1, 356	1, 348
Cumulative amount of study drug administered up to Week 24 (mg)		
n	309	307
Mean (SD)	3.24 (0.569)	3.26 (0.571)
Median	3.50	3.50
Min, Max	0.5, 3.5	0.5, 3.5
Cumulative amount of study drug administered up to Week 52 (mg)		
n	309	307
Mean (SD)	5.85 (1.246)	5.87 (1.308)
Median	6.50	6.50
Min, Max	0.5, 6.5	0.5, 6.5

Source: Table 11 (Table 14.3.4.4) of final updated QL1205-002 CSR

Similar amounts of study drug were administered to patients in both treatment arms, no notable differences were observed.

The main reason for not completing the study treatment up to Week 24 was subject withdrawal of consent (9 subjects, 1.5%), followed by AE and other reasons (5 subjects each, 0.8%). Of the 616 randomised subjects, 44 subjects (7.1%) discontinued the study prematurely as of the data cut-off of 27 Jan 2022 (n=17 in the Rimmyrah arm, n=27 in the Lucentis arm), mainly because of withdrawal of consent (18 subjects, 2.9%), followed by AE and other reasons (10 subjects each, 1.6%).

3 patients in the Rimmyrah arm and 7 patients in the EU-Lucentis arm discontinued the study prematurely due to "other reasons" until DCO. The applicant clarified the "other" reasons leading to premature study discontinuation until DCO for IA. Those reasons were mainly the COVD-19 pandemic, death, refusal to visit or to continue, as well as "personal" reasons. Furthermore, an updated subject disposition table has been provided with the final updated CSR, with all randomized participants included (final data set). Here, an exhaustive list of the reasons for premature study discontinuation is included. No notable differences or imbalances between the treatment arms were noted.

Supportive Phase 1 study QL1205-001

In the supportive Phase 1 study, 48 Chinese subjects were randomised. A total of 46 (95.8%) subjects completed the study, 2 subjects had withdrawn from the study: 1 subject from the Rimmyrah treatment groups and 1 subject from Lucentis treatment group prematurely.

Each enrolled subject received intravitreal injection once every 4 weeks for 3 doses in the form of either Rimmyrah or Lucentis according to the randomisation list. In total, 23 subjects received Rimmyrah and 25 subjects received Lucentis.

The mean age of subjects was 68.3 (7.34) years old in the Rimmyrah treatment group and 63.4 (5.36) years old in the Lucentis treatment group. The majority of subjects were male, 17 (73.9%) subjects in the Rimmyrah treatment group and 18 (72%) subjects in Lucentis treatment group. The baseline demographic characteristics of the two treatment groups were comparable.

Table 43. Demographic characteristics – FAS (QL1205-001)

	QL1205 (N = 23)	Lucentis (N = 25)
Age (years)		
Mean (SD)	68.3 (7.34)	63.4 (5.36)
Median (Q1, Q3)	68.0 (63.0, 75.0)	63.0 (58.0, 68.0)
Min, Max	54, 80	55, 73
Gender		
Male	17 (73.9%)	18 (72.0%)
Female	6 (26.1%)	7 (28.0%)
Ethnicity, n (%)		
Han Chinese	23 (100.0%)	25 (100.0%)
Other	0 (0.0%)	0 (0.0%)
Height (cm)		
Mean (SD)	164.63 (7.255)	166.20 (8.211)
Median (Q1, Q3)	165.00 (157.50, 169.00)	166.00 (160.00, 173.00)
Min, Max	151.0, 178.0	149.0, 181.0
Weight (kg)		
Mean (SD)	64.67 (11.413)	66.26 (11.646)
Median (Q1, Q3)	63.00 (55.00, 74.70)	65.00 (60.00, 75.00)
Min, Max	46.0, 86.5	41.0, 90.0

Note: Percentages are calculated using the number of cases in each group as the denominator for all items.
Source: CSR Phase 1 QL1205-001 Listing 14.1.2.1

The baseline characteristics of subjects in the two groups were comparable. There were 21 (91.3%) subjects in the Rimmyrah treatment group and 21 (84.0%) subjects in the Lucentis treatment group who had ocular and systemic conditions other than AMD. All subjects had wAMD in the study eye. Six subjects had wAMD in the fellow eye, 2 (8.7%) in the Rimmyrah treatment group and 4 (16%) subjects in the Lucentis treatment group. Eight subjects had a history of previous treatment for wAMD, 6 (26.1%) subjects in the Lucentis treatment group and 2 (8.0%) subjects in the Rimmyrah treatment group.

Most subjects received at least one concomitant medication: 18 (78.3%) subjects in Rimmyrah treatment group, and 16 (64.0%) subjects in the Lucentis treatment group.

A total of 59 subjects were screened, of which 48 subjects were randomised. A total of 46 (95.8%) subjects completed the study, 2 subjects had withdrawn from the study: 1 subject from the Rimmyrah treatment groups and 1 subject from Lucentis treatment group prematurely. The reason for withdrawal was SAE in the Rimmyrah treatment group, and the reason for withdrawal in Lucentis treatment group was investigator-considered withdrawal from trial in consideration of subject safety.

All 48 subjects in both Rimmyrah and Lucentis groups received 3 doses during the study.

Table 44. Drug Exposure (FAS)

	QL1205 (N = 23)	Lucentis (N = 25)
Number of Doses		
N	23	25
Mean (SD)	3.0 (0.00)	3.0 (0.00)
Median (Q1, Q3)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
Min, Max	3, 3	3, 3

Source: Table 14.3.1.1

Each enrolled subject received intravitreal injection once every 4 weeks for 3 doses in the form of either Rimmyrah or Lucentis according to the randomisation list. In total, 23 subjects received Rimmyrah and 25 subjects received Lucentis. Treatment compliance is summarised in Table 45 (Table 2.7.4- 2) in the FAS.

Table 45. Drug Exposure - FAS

	Lucentis (N=23)	QL1205 (N=25)
Number of doses		
N	23	25
Mean (SD)	3.0 (0.00)	3.0 (0.00)
Median (Q1, Q3)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
Min, Max	3, 3	3, 3

Source: CSR Phase 1 QL1205-001 Listing 14.3.1.1

2.4.9.2. Adverse events

Pivotal Phase 3 study QL1205-002

All safety analyses were performed for the SAF (Safety Set). The SAF consisted of all randomized subjects who received at least 1 administration of study drug. In the SAF, all subjects are analysed under the actual treatment received.

AEs were classified as "ocular AEs" and "non-ocular AEs". For ocular AEs, a distinction was made between study eye and fellow eye.

Treatment-emergent AEs (TEAE) were defined as events that were newly occurring or worsening from the time of the first dose of study drug.

Adverse event overview

The overall number and percentage of TEAE reported up to the interim cut-off date of 27 January 2022 was comparable between the two treatment groups: 71.8% of the patients in the Rimmyrah group experienced 656 events and 69.7% of the patients in the Lucentis group experienced 625 events.

Table 46. Treatment-Emergent Adverse Events – Overall Summary – Safety Set

	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
At least 1 TEAE	222	656	71.8	214	625	69.7	436	1281	70.8
Study eye	104	161	33.7	99	162	32.2	203	323	33.0
Fellow eye	45	54	14.6	43	59	14.0	88	113	14.3
Non-Ocular	172	458	55.7	165	414	53.7	337	872	54.7
At least 1 mild TEAE	194	487	62.8	179	443	58.3	373	930	60.6
Study eye	88	128	28.5	83	134	27.0	171	262	27.8
Fellow eye	33	35	10.7	25	29	8.1	58	64	9.4
Non-Ocular	148	337	47.9	136	287	44.3	284	624	46.1
At least 1 moderate TEAE	73	139	23.6	80	155	26.1	153	294	24.8
Study eye	23	29	7.4	17	21	5.5	40	50	6.5
Fellow eye	16	18	5.2	23	30	7.5	39	48	6.3
Non-Ocular	52	96	16.8	55	107	17.9	107	203	17.4
At least 1 severe TEAE	23	30	7.4	18	27	5.9	41	57	6.7
Study eye	4	4	1.3	4	7	1.3	8	11	1.3
Fellow eye	1	1	0.3	0	0	0	1	1	0.2
Non-Ocular	18	25	5.8	14	20	4.6	32	45	5.2
At least 1 related to study treatment TEAE	17	20	5.5	21	32	6.8	38	52	6.2
Study eye	14	17	4.5	20	28	6.5	34	45	5.5
Fellow eye	1	2	0.3	0	0	0	1	2	0.2
Non-Ocular	3	3	1.0	2	4	0.7	5	7	0.8
At least 1 related to protocol-required procedure TEAE	33	42	10.7	41	59	13.4	74	101	12.0
Study eye	32	41	10.4	36	53	11.7	68	94	11.0
Fellow eye	2	3	0.6	2	2	0.7	4	5	0.6
Non-Ocular	1	1	0.3	4	5	1.3	5	6	0.8
At least 1 serious TEAE	28	44	9.1	19	28	6.2	47	72	7.6
Study eye	4	4	1.3	1	1	0.3	5	5	0.8
Fellow eye	0	0	0	0	0	0	0	0	0
Non-Ocular	24	40	7.8	19	27	6.2	43	67	7.0
At least 1 TEAE leading to discontinuation	5	7	1.6	8	9	2.6	13	16	2.1
Study eye	2	2	0.6	3	4	1.0	5	6	0.8
Fellow eye	0	0	0	0	0	0	0	0	0
Non-Ocular	3	5	1.0	5	5	1.6	8	10	1.3
At least 1 TEAE leading to death	5	9	1.6	3	6	1.0	8	15	1.3
Study eye	0	0	0	0	0	0	0	0	0
Fellow eye	0	0	0	0	0	0	0	0	0
Non-Ocular	5	9	1.6	3	6	1.0	8	15	1.3

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.
Source: Table 14.3.1.1

TEAE by SOC & PT

The most commonly affected SOCs in both treatment groups in the SAF were Eye disorders, Infections and infestations, and Investigations. Overall, the SOC Eye disorders was the most commonly affected SOC for both treatment arms in the SAF (QL1205: 37.2% of patients with 173 events; Lucentis: 35.2% of patients with 175 events). The most commonly affected PTs in this SOC were Neovascular

age-related macular degeneration (QL1205: 4.5%; Lucentis: 3.3%), Visual acuity reduced (QL1205: 3.2%; Lucentis: 3.9%), and Conjunctival hemorrhage (QL1205: 3.6%; Lucentis: 2.6%).

Other commonly affected PTs were Hypertension from SOC Infections and Infestations (QL1205: 5.5%; Lucentis: 7.5%) and IOP increased from SOC Investigations (QL1205: 3.9%; Lucentis: 2.6%).

Table 47. Treatment-Emergent Adverse Events Which Occurred in ≥1.0% of Subjects Overall by System Organ Class and Preferred Term – All - SS

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Number of subjects with at least 1 TEAE	**222**	**656**	**71.8**	**214**	**625**	**69.7**	**436**	**1281**	**70.8**
Eye disorders	**115**	**173**	**37.2**	**108**	**175**	**35.2**	**223**	**348**	**36.2**
Neovascular age-related macular degeneration	14	15	4.5	10	10	3.3	24	25	3.9
Visual acuity reduced	10	12	3.2	12	15	3.9	22	27	3.6
Conjunctival haemorrhage	11	13	3.6	8	13	2.6	19	26	3.1
Macular fibrosis	8	8	2.6	9	9	2.9	17	17	2.8
Retinal haemorrhage	9	10	2.9	7	7	2.3	16	17	2.6
Cataract	8	8	2.6	5	5	1.6	13	13	2.1
Foreign body sensation in eyes	5	5	1.6	8	9	2.6	13	14	2.1
Retinal pigment epitheliopathy	6	6	1.9	6	6	2.0	12	12	1.9
Subretinal fluid	3	4	1.0	9	10	2.9	12	14	1.9
Macular oedema	6	6	1.9	5	5	1.6	11	11	1.8
Dry eye	7	7	2.3	2	2	0.7	9	9	1.5
Cataract nuclear	3	3	1.0	5	5	1.6	8	8	1.3
Visual impairment	5	5	1.6	3	5	1.0	8	10	1.3
Macular scar	5	5	1.6	2	2	0.7	7	7	1.1
Posterior capsule opacification	2	2	0.6	5	5	1.6	7	7	1.1
Vitreous floaters	0	0	0	7	7	2.3	7	7	1.1
Blindness	5	5	1.6	1	1	0.3	6	6	1.0
Cataract cortical	4	4	1.3	2	2	0.7	6	6	1.0
Infections and infestations	**69**	**98**	**22.3**	**58**	**74**	**18.9**	**127**	**172**	**20.6**
Nasopharyngitis	10	10	3.2	10	10	3.3	20	20	3.2
Urinary tract infection	12	19	3.9	7	9	2.3	19	28	3.1
Rhinitis	7	7	2.3	9	9	2.9	16	16	2.6
COVID-19	10	12	3.2	4	4	1.3	14	16	2.3
Upper respiratory tract infection	7	8	2.3	7	11	2.3	14	19	2.3
Conjunctivitis	4	4	1.3	6	6	2.0	10	10	1.6
Pneumonia	5	6	1.6	2	3	0.7	7	9	1.1
Investigations	**54**	**91**	**17.5**	**38**	**78**	**12.4**	**92**	**169**	**14.9**
Intraocular pressure increased	12	15	3.9	8	12	2.6	20	27	3.2
Blood glucose increased	10	10	3.2	6	8	2.0	16	18	2.6
Blood pressure increased	10	12	3.2	6	7	2.0	16	19	2.6
Protein urine present	8	10	2.6	4	8	1.3	12	18	1.9
SARS-CoV-2 test positive	3	3	1.0	3	3	1.0	6	6	1.0
Gastrointestinal disorders	**23**	**27**	**7.4**	**28**	**44**	**9.1**	**51**	**71**	**8.3**
Toothache	6	7	1.9	10	11	3.3	16	18	2.6
Diarrhoea	0	0	0	6	7	2.0	6	7	1.0

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Musculoskeletal and connective tissue disorders	**23**	**38**	**7.4**	**26**	**37**	**8.5**	**49**	**75**	**8.0**
Back pain	12	18	3.9	11	17	3.6	23	35	3.7
Arthralgia	5	5	1.6	1	1	0.3	6	6	1.0
Vascular disorders	**19**	**22**	**6.1**	**27**	**32**	**8.8**	**46**	**54**	**7.5**
Hypertension	17	17	5.5	23	25	7.5	40	42	6.5
Nervous system disorders	**23**	**33**	**7.4**	**19**	**30**	**6.2**	**42**	**63**	**6.8**
Headache	11	15	3.6	8	13	2.6	19	28	3.1
Dizziness	3	3	1.0	5	5	1.6	8	8	1.3
Respiratory, thoracic and mediastinal disorders	**22**	**27**	**7.1**	**20**	**24**	**6.5**	**42**	**51**	**6.8**
Cough	7	7	2.3	6	6	2.0	13	13	2.1
Metabolism and nutrition disorders	**24**	**28**	**7.8**	**12**	**15**	**3.9**	**36**	**43**	**5.8**
Hyperglycaemia	7	7	2.3	1	1	0.3	8	8	1.3
Diabetes mellitus	4	5	1.3	2	2	0.7	6	7	1.0
General disorders and administration site conditions	**14**	**17**	**4.5**	**17**	**26**	**5.5**	**31**	**43**	**5.0**
Pyrexia	6	7	1.9	9	9	2.9	15	16	2.4
Injury, poisoning and procedural complications	**16**	**19**	**5.2**	**14**	**15**	**4.6**	**30**	**34**	**4.9**
Ligament sprain	3	3	1.0	3	3	1.0	6	6	1.0
Ear and labyrinth disorders	**3**	**5**	**1.0**	**8**	**8**	**2.6**	**11**	**13**	**1.8**
Vertigo	3	5	1.0	5	5	1.6	8	10	1.3
Reproductive system and breast disorders	**4**	**5**	**1.3**	**3**	**3**	**1.0**	**7**	**8**	**1.1**
Benign prostatic hyperplasia	3	3	1.0	3	3	1.0	6	6	1.0

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that were newly occurring or worsening from the time of the first dose of study drug.
Source: CSR Phase 3 QL1205-002 Table 14.3.1.2.1

Ocular TEAE in study eye

Frequencies of ocular TEAE in the study were overall comparable between both treatment groups. Overall, 161 events occurred in 104 subjects in the Rimmyrah group (33.7%) compared to 162 events in 99 subjects in the Lucentis group (32.2%).

The most frequently occurring TEAE by SOC were Eye disorders (QL1205: 29.8%, Lucentis: 28.7%), Investigations (QL1205: 3.6%, Lucentis: 2.6%), and Infections and infestations (QL1205: 2.3%, Lucentis: 2.6%). The most frequently occurring TEAE by PT were Conjunctival haemorrhage (QL1205: 3.6%, Lucentis: 2.6%), IOP increased (QL1205: 3.6%, Lucentis: 2.6%), and Macular fibrosis (QL1205: 2.6%, Lucentis: 2.9%). The incidences of the PT´s Dry eye, Macular scar, Blindness, and Cataract cortical were higher in Rimmyrah group in comparison to Lucentis group. The applicant was requested to discuss these findings.

The applicant has provided a list of treatment-emergent adverse events for the study eye specifically. Higher incidence of macular scar in the Rimmyrah group compared to Lucentis group was justified by the natural progression of the disease. Moreover, diagnosis of macular scar seems to be subjective and differentiates between the investigators. The applicant has also submitted a list of these adverse events that were considered to be related to the study drug. In this list, the number of events is lower and the differences between the Rimmyrah and Lucentis group are negligible. This justification is considered acceptable.

Table 48. Treatment-Emergent Adverse Events Which Occurred in ≥1.0% of Subjects Overall by System Organ Class and Preferred Term – Study Eye – Safety Set

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Number of subjects with at least 1 TEAE	104	161	33.7	99	162	32.2	203	323	33.0
Eye disorders	92	138	29.8	88	130	28.7	180	268	29.2
Conjunctival haemorrhage	11	13	3.6	8	13	2.6	19	26	3.1
Macular fibrosis	8	8	2.6	9	9	2.9	17	17	2.8
Visual acuity reduced	9	11	2.9	7	9	2.3	16	20	2.6
Retinal haemorrhage	8	9	2.6	6	6	2.0	14	15	2.3
Foreign body sensation in eyes	5	5	1.6	7	7	2.3	12	12	1.9
Retinal pigment epitheliopathy	6	6	1.9	6	6	2.0	12	12	1.9
Cataract	5	5	1.6	4	4	1.3	9	9	1.5
Macular oedema	5	5	1.6	4	4	1.3	9	9	1.5
Subretinal fluid	2	2	0.6	7	7	2.3	9	9	1.5
Cataract nuclear	3	3	1.0	5	5	1.6	8	8	1.3
Dry eye	7	7	2.3	1	1	0.3	8	8	1.3
Macular scar	5	5	1.6	2	2	0.7	7	7	1.1
Visual impairment	4	4	1.3	3	4	1.0	7	8	1.1
Posterior capsule opacification	2	2	0.6	4	4	1.3	6	6	1.0
Vitreous floaters	0	0	0	6	6	2.0	6	6	1.0
Investigations	11	14	3.6	8	13	2.6	19	27	3.1
Intraocular pressure increased	11	14	3.6	8	12	2.6	19	26	3.1
Infections and infestations	7	8	2.3	8	10	2.6	15	18	2.4
Conjunctivitis	3	3	1.0	6	6	2.0	9	9	1.5

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.
Source: Table 14.3.1.2.2

When analyzed for the subgroup "Region - Europe", ocular TEAE in the study eye were reported from 64 subjects (34.6%) in the Rimmyrah arm and from 63 subjects (34.6%) in the EU-Lucentis arm. The most frequently reported ocular TEAE in the study eye for the European subgroup by PT were macular fibrosis (QL1205: 4.3% vs. Lucentis: 4.9%) and visual acuity reduced (4.9% vs 3.8%).

According to the Lucentis SmPC, the most frequently reported ocular adverse reactions following Lucentis injection are: eye pain, ocular hyperaemia, increased intraocular pressure, vitreous detachment, retinal haemorrhage, visual disturbance, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus. However, in the pivotal Phase 3 study, macular fibrosis was one of the most frequently reported TEAE by PT with incidences of 2.6% (n=8 events in the Rimmyrah arm) and 2.9% (n=9 events in the Lucentis arm). The applicant was requested to discuss the imbalance between the ocular safety profile outlined in the Lucentis SmPC and the reported ocular TEAE by PT in the pivotal study.

The applicant stressed that the formation of subretinal/ macular fibrosis occurs in the natural course of the wAMD disease as a wound healing response to CNV. This is acknowledged. It is well-known that anti-VEGF therapy can only delay the formation of fibrosis, but does not necessarily prevent it.

Thus, typically subretinal fibrosis is not per se an adverse event, but part of the natural course of the wAMD disease progression.

It was outlined by the applicant that, in study QL1205-002, macular fibrosis has been reported as an Adverse Event at three study sites for some patients as a potential cause for the no improvement in Visual Acuity (Site: 14 cases - 82% of total reported: 2 cases - 12% of total reported: 1 case - 6% of total reported).

In addition, degenerative retinal processes have been also described as adverse reaction for the originator, however by another PT (adverse reaction "retinal degeneration" with frequency "common", see SmPC).

Ocular TEAE in fellow eye

A total of 113 TEAE occurred in the fellow eye for 88 subjects (14.3%), with 54 events in 45 subjects in the Rimmyrah group (14.6%) and 59 events in 43 subjects in the Lucentis group (14.0%). Most TEAE in the fellow eye fall under the SOC of Eye disorders (QL1205: 13.9%, Lucentis: 12.4%). TEAE in the fellow eye that occurred in ≥1.0% of subjects were Neovascular age-related macular degeneration (QL1205: 4.2%, Lucentis: 3.3%), Visual acuity reduced (QL1205: 0.3%, Lucentis: 2.3%), and Dry eye (QL1205: 1.6%, Lucentis: 0.3%).

Table 49. Treatment-Emergent Adverse Events Which Occurred in ≥1.0% of Subjects Overall by System Organ Class and Preferred Term – Fellow Eye – Safety Set

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Number of subjects with at least 1 TEAE	45	54	14.6	43	59	14.0	88	113	14.3
Eye disorders	43	52	13.9	38	51	12.4	81	103	13.1
Neovascular age-related macular degeneration	13	14	4.2	10	10	3.3	23	24	3.7
Visual acuity reduced	1	1	0.3	7	7	2.3	8	8	1.3
Dry eye	5	5	1.6	1	1	0.3	6	6	1.0

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.
Source: Table 14.3.1.2.3

Non-ocular TEAE

Frequencies of non-ocular (i.e. systemic) TEAE in the study were overall comparable between both treatment groups, and no clinically relevant differences were identified. Overall, 458 events occurred in 172 subjects in the Rimmyrah group (55.7%) compared to 414 events in 165 subjects in the Lucentis group (53.7%).

The most frequently occurring non-ocular TEAE by SOC were Infections and infestations QL1205: 20.1%, Lucentis: 16.6%), Investigations (QL1205: 13.6%, Lucentis: 10.1%), and Gastrointestinal disorders (QL1205: 7.4%, Lucentis: 9.1%). The most frequently occurring TEAE by PT (≥3.0% in any group) were Hypertension (QL1205: 5.5%, Lucentis: 7.5%), Back pain (QL1205: 3.9%, Lucentis: 3.6%), Nasopharyngitis (QL1205: 3.2%, Lucentis: 3.3%), Headache (QL1205: 3.6%, Lucentis: 2.6%), Urinary tract infection (QL1205: 3.9%, Lucentis: 2.3%), Blood glucose increased (QL1205: 3.2%, Lucentis: 2.0%), Blood pressure increased (QL1205: 3.2%, Lucentis: 2.0%), Toothache (QL1205: 1.9%, Lucentis: 3.3%), and COVID-19 (QL1205: 3.2%, Lucentis: 1.3%).

Table 50. Treatment-Emergent Adverse Events Which Occurred in ≥1.0% of Subjects Overall by System Organ Class and Preferred Term – Non-Ocular – Safety Set

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Number of subjects with at least 1 TEAE	172	458	55.7	165	414	53.7	337	872	54.7
Infections and infestations	62	89	20.1	51	63	16.6	113	152	18.3
Nasopharyngitis	10	10	3.2	10	10	3.3	20	20	3.2
Urinary tract infection	12	19	3.9	7	9	2.3	19	28	3.1
Rhinitis	7	7	2.3	9	9	2.9	16	16	2.6
COVID-19	10	12	3.2	4	4	1.3	14	16	2.3
Upper respiratory tract infection	7	8	2.3	7	11	2.3	14	19	2.3
Pneumonia	5	6	1.6	2	3	0.7	7	9	1.1
Investigations	42	76	13.6	31	65	10.1	73	141	11.9
Blood glucose increased	10	10	3.2	6	8	2.0	16	18	2.6
Blood pressure increased	10	12	3.2	6	7	2.0	16	19	2.6
Protein urine present	8	10	2.6	4	8	1.3	12	18	1.9
SARS-CoV-2 test positive	3	3	1.0	3	3	1.0	6	6	1.0
Gastrointestinal disorders	23	27	7.4	28	44	9.1	51	71	8.3
Toothache	6	7	1.9	10	11	3.3	16	18	2.6
Diarrhoea	0	0	0	6	7	2.0	6	7	1.0
Musculoskeletal and connective tissue disorders	23	38	7.4	26	37	8.5	49	75	8.0
Back pain	12	18	3.9	11	17	3.6	23	35	3.7
Arthralgia	5	5	1.6	1	1	0.3	6	6	1.0
Vascular disorders	19	22	6.1	27	32	8.8	46	54	7.5
Hypertension	17	17	5.5	23	25	7.5	40	42	6.5
Nervous system disorders	23	33	7.4	19	30	6.2	42	63	6.8
Headache	11	15	3.6	8	13	2.6	19	28	3.1
Dizziness	3	3	1.0	5	5	1.6	8	8	1.3
Respiratory, thoracic and mediastinal disorders	22	27	7.1	20	24	6.5	42	51	6.8
Cough	7	7	2.3	6	6	2.0	13	13	2.1
Metabolism and nutrition disorders	24	28	7.8	12	15	3.9	36	43	5.8
Hyperglycaemia	7	7	2.3	1	1	0.3	8	8	1.3
Diabetes mellitus	4	5	1.3	2	2	0.7	6	7	1.0
General disorders and administration site conditions	13	16	4.2	16	22	5.2	29	38	4.7
Pyrexia	6	7	1.9	9	9	2.9	15	16	2.4
Injury, poisoning and procedural complications	16	19	5.2	12	13	3.9	28	32	4.5
Ligament sprain	3	3	1.0	3	3	1.0	6	6	1.0
Ear and labyrinth disorders	3	5	1.0	8	8	2.6	11	13	1.8
Vertigo	3	5	1.0	5	5	1.6	8	10	1.3
Reproductive system and breast disorders	4	5	1.3	3	3	1.0	7	8	1.1
Benign prostatic hyperplasia	3	3	1.0	3	3	1.0	6	6	1.0

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.
Source: Table 14.3.1.2.4

Injection site reactions

Frequencies of injection site reactions were overall comparable between the study arms: 43 events occurred in 35 subjects in the Rimmyrah group (11.3%), whereas 63 events occurred in 41 subjects in the Lucentis group (13.4%).

Injection site reactions which occurred in ≥1.0% of subjects included Conjunctival haemorrhage (QL1205: 3.2%, Lucentis: 2.3%), Foreign body sensation in eyes (QL1205: 1.6%, Lucentis: 2.3%), and IOP increased (QL1205: 2.3%, Lucentis: 1.6%).

Table 51. Treatment-Emergent Adverse Events Which Occurred in ≥1.0% of Subjects Overall by System Organ Class and Preferred Term – Injection Site Reactions – Safety Set

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Number of subjects with at least 1 TEAE	35	43	11.3	41	63	13.4	76	106	12.3
Eye disorders	27	32	8.7	33	44	10.7	60	76	9.7
Conjunctival haemorrhage	10	12	3.2	7	12	2.3	17	24	2.8
Foreign body sensation in eyes	5	5	1.6	7	7	2.3	12	12	1.9
Investigations	7	9	2.3	5	9	1.6	12	18	1.9
Intraocular pressure increased	7	9	2.3	5	9	1.6	12	18	1.9

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.
Source: Table 14.3.1.11.1

All injections site reactions occurred in the study eye, except for 2 events that occurred in the fellow eye in 2 subjects in the Lucentis group: Foreign body sensation in eyes and an uncoded event – noted to be an event of binocular dry eye.

It has been clarified by the applicant that, for events of conjunctival hemorrhage and raised IOP, a medical query was issued to the sites to confirm whether the events were injection site reactions or not. Here, the following definitions were used:

Injection site reactions (ISR) are a local phenomenon defined as a constellation of symptoms, including swelling, erythema, pruritus, and pain around the site of injection. They develop during or immediately after the IVT procedure.

The classification TEAE would include any adverse event related to the treatment period, not just related to the injection site and IVT procedure. This implies are larger group than the ISR.

TEAE related to study drug

Overall, only a small number of TEAE was considered to be study-drug related: A total of 38 subjects (6.2%) experienced 52 treatment-related TEAE, with comparable numbers for both treatment arms (QL1205: 20 events in 17 subjects [5.5%]; Lucentis: 32 events in 21 subjects [6.8%]). Most treatment-related TEAE were under the SOC of Eye disorders (QL1205: 3.2%, Lucentis: 4.9%) and Investigations (QL1205: 1.6%, Lucentis: 1.3%).

Tabulated summaries comparing the numbers of study-drug related TEAE in the study eye as well as treatment-related non-ocular TEAE have been provided, as requested, also by SOC and PT. No notable differences between biosimilar and originator were observed.

Overall, 34 subjects (5.5%) experienced 45 treatment-related TEAE in the study eye, with comparable frequencies for both treatment arms (QL1205: 17 events in 14 subjects [4.5%]; Lucentis: 28 events in 20 subjects [6.5%]). Most treatment-related TEAE in the study eye were under the SOC of Eye disorders (QL1205: 3.2%, Lucentis: 4.9%) and Investigations (QL1205: 1.3%, Lucentis: 1.3%). All treatment-related TEAE in the study eye occurred in <1.0% of subjects, except for IOP increased (1.3% in both treatment arms).

One subject in the Rimmyrah arm (0.3%) experienced 2 treatment-related TEAE in the fellow eye: dry eye and eye pruritus.

With regard to treatment-related non-ocular TEAE, overall 5 subjects experienced 7 events. Frequencies were balanced between treatment arms with 3 events (Hypertensive heart disease, Vertigo, Blood glucose increased) in 3 subjects (1.0%) in the Rimmyrah arm and 4 events (Upper respiratory tract infection [2 events], Osteitis, and Insomnia) in 2 subjects (0.7%) in the Lucentis arm.

TEAE related to protocol-required procedures

All TEAE with a reasonable causal relationship to any protocol-required procedure were classified in this category. Numerically higher numbers of TEAE related to protocol-required procedures were observed in the Lucentis arm (59 events in 41 subjects [13.4%], compared to 42 events in 33 subjects in the Rimmyrah arm [10.7%]).

Most TEAE related to protocol-required procedures were under the SOC of Eye disorders (QL1205: 7.4%, Lucentis: 9.4%) and Investigations (QL1205: 2.9%, Lucentis: 1.6%). Importantly, most TEAE related to protocol-required procedures occurred in <1.0% of subjects, except for Conjunctival haemorrhage (QL1205: 3.6%, Lucentis: 2.6%), Foreign body sensation in eyes (QL1205: 1.6%, Lucentis: 2.0%), and IOP increased (QL1205: 2.9%, Lucentis: 1.6%).

With regard to TEAE in the study eye related to protocol-required procedures, the frequencies were overall comparable with 41 events in 32 subjects in the Rimmyrah group (10.4%)] and 53 events in 36 subjects in the Lucentis group (11.7%). Most TEAE in the study eye related to protocol-required procedures were under the SOC of Eye disorders (QL1205: 7.4%, Lucentis: 9.1%) and Investigations (QL1205: 2.9%, Lucentis: 1.6%).

TEAE in the fellow-eye related to protocol-required procedures were rare and comparable between treatment arms (0.6% in both study arms).

Overall, 5 subjects (0.8%) experienced 6 non-ocular TEAE related to protocol-required procedures (1 event of Vertigo in 1 subject in the Rimmyrah group [0.3%] and 5 events (Nausea [2 events], Retching, Back pain, Dermatitis) in 4 subjects in the Lucentis group [1.3%]).

TEAE by severity

Overall, most TEAE were of mild (QL1205: 45.6%; Lucentis: 41.0%) or moderate intensity (QL1205: 18.8%; Lucentis: 22.8%); only a few severe TEAE were reported (QL1205: 7.4%; Lucentis: 5.9%).

With regard to ocular TEAE in the study eye, most TEAE were mild (QL1205: 25.9%; Lucentis: 25.7%) or moderate (QL1205: 5.2%; Lucentis: 7.5%). Severe TEAE in the study eye occurred in 1.3% of subjects in both groups.

In the fellow eye, most TEAE were mild (QL1205: 9.1%, Lucentis: 6.5%) or moderate (QL1205: 5.2%, Lucentis: 7.5%). A severe TEAE of cataract in the fellow eye occurred in 1 subject in the Rimmyrah group (0.3%).

Most non-ocular TEAE were mild (QL1205: 36.2%, Lucentis: 34.2%) or moderate (QL1205: 13.6%, Lucentis: 15.0%). Severe non-ocular TEAE occurred in 5.8% of subjects in the Rimmyrah group and in 4.6% of subjects in the Lucentis group.

Severe TEAE occurred in 7.4% of QL1205-treated subjects and in 5.9% of Lucentis-treated subjects.

Severe TEAE in the study eye were reported from 1.3% of patients for both Rimmyrah and Lucentis treatment arms. Only 1 severe TEAE in the fellow eye was reported from 1 subject in the Rimmyrah arm (0.3%). Severe non-ocular TEAE occurred in 5.8% of the QL1205-treated subjets compared to 4.6% of the Lucentis-treated subjects.

Only few severe TEAE were judged related to study treatment – they all occurred in the study eye: 2 events occurred in 1 patient (0.3%) in the Rimmyrah arm (1 event of retinal haemorrhage, 1 event of vitreous haemorrhage), and 6 events occurred in 3 patients (1.0%) in the Lucentis arm (retinal haemorrhage, RPE detachment, macular oedema, subretinal fluid, 2 events of endophthalmitis).

Overall, no notable imbalances were seen with regard to the occurrence of severe TEAE, including related ones, between the treatment arms.

Supportive Phase 1 study QL1205-001

In the supportive Phase 1 study in Chinese patients, 28 of 48 subjects (58.3%) reported 90 TEAE during the study: 15 (65.2%) subjects reported 54 TEAE in the Rimmyrah group and 13 (52%) subjects reported 36 TEAE in the Lucentis group. There was thus a numerical imbalance regarding the overall frequency of TEAE observed.

However, the majority of TEAE was mild to moderate in intensity, with only 2 subjects in the Rimmyrah am reporting severe TEAE that were considered unrelated to the IMP (1 Arrhythmia, 1 Pancreatic carcinoma).

Overall, 8 events were reported to be related to the study drug in 3 (13%) subjects in the Rimmyrah group, and 1 TEAE was reported to be related in 1 (4%) subject in the Lucentis group.

Table 52

Table 2.7.4-9 Ocular and non-ocular TEAE - SS

	QL1205 (N = 23)						Lucentis (N = 25)					
	Ocular		Non-ocular		Total		Ocular		Non-ocular		Total	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Number (of) subjects with at least 1TEAE	7 (30.4)	15	13 (56.5)	39	15 (65.2)	54	4 (16.0)	7	12 (48.0)	29	13 (52.0)	36
TEAEs related to trial drug	1 (4.3)	3	2 (8.7)	5	3 (13.0)	8	1 (4.0)	1	0 (0.0)	0	1 (4.0)	1
Serious Adverse Events	0 (0.0)	0	2 (8.7)	2	2 (8.7)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious (sight-threatening) ocular adverse events	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAEs Leading to Subject Death	0 (0.0)	0	1 (4.3)	1	1 (4.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAEs Leading to Withdrawal	0 (0.0)	0	1 (4.3)	1	1 (4.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Source: CSR Phase 1 QL1205-001 Listing 14.3.1.2

Table 2.7.4-10 Ocular TEAE in the target and non-target eye - SS

	QL1205 (N = 23)						Lucentis (N = 25)					
	Study eye		Fellow eye		Total		Study eye		Fellow eye		Total	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
All TEAEs	7 (30.4)	12	3 (13.0)	3	7 (30.4)	15	4 (16.0)	5	2 (8.0)	2	4 (16.0)	7
TEAEs related to trial drug	1 (4.3)	3	0 (0.0)	0	1 (4.3)	3	1 (4.0)	1	0 (0.0)	0	1 (4.0)	1
Serious Adverse Events	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious ocular adverse events	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAEs Leading to Subject Death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAEs Leading to Withdrawal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Source: CSR Phase 1 QL1205-001 Listing 14.3.1.3

At the PT level, the reported TEAE related to the study drug in the Rimmyrah group were Ocular hypertension, Activated partial thromboplastin time ratio decreased, Electrocardiogram Q wave abnormal, Pyrexia, and Sinus tachycardia. The reported TEAE by PT related to the IMP in the Lucentis arm was dry eye.

2.4.9.3. Serious adverse events, deaths, and other significant events

Pivotal Phase 3 study QL1205-002

Overall SAE

Frequencies of SAE reported up to the interim cut-off date of 27 January 2022 were overall low in the pivotal Phase 3 study: A total of 47 patients (7.6%) experienced 72 SAE. However, a numerically higher number of patients (n=28 [9.1%] with 44 events) in the Rimmyrah group experienced a serious TEAE than in the Lucentis group (n=19 [6.2%] with 28 events). Importantly, all serious TEAE occurred in <1% of subjects overall, and most were non-ocular events.

Table 53. Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – All – Safety Set

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Number of subjects with at least 1 serious TEAE	28	44	9.1	19	28	6.2	47	72	7.6
Infections and infestations	13	16	4.2	4	5	1.3	17	21	2.8
COVID-19	5	5	1.6	0	0	0	5	5	0.8
Pneumonia	4	4	1.3	1	2	0.3	5	6	0.8
COVID-19 pneumonia	1	1	0.3	1	1	0.3	2	2	0.3
Endophthalmitis	1	1	0.3	1	1	0.3	2	2	0.3
Chikungunya virus infection	1	1	0.3	0	0	0	1	1	0.2
Pneumonia viral	1	1	0.3	0	0	0	1	1	0.2
Post-acute COVID-19 syndrome	1	1	0.3	0	0	0	1	1	0.2
Sepsis	0	0	0	1	1	0.3	1	1	0.2
Septic shock	1	1	0.3	0	0	0	1	1	0.2
Urosepsis	1	1	0.3	0	0	0	1	1	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	3	1.0	6	6	2.0	9	9	1.5
Breast cancer	1	1	0.3	1	1	0.3	2	2	0.3
Basal cell carcinoma	0	0	0	1	1	0.3	1	1	0.2
Bladder cancer	0	0	0	1	1	0.3	1	1	0.2
Colon cancer	1	1	0.3	0	0	0	1	1	0.2
Gastric cancer	0	0	0	1	1	0.3	1	1	0.2
Lung adenocarcinoma	0	0	0	1	1	0.3	1	1	0.2
Meningioma	1	1	0.3	0	0	0	1	1	0.2
Metastasis	0	0	0	1	1	0.3	1	1	0.2
Nervous system disorders	4	5	1.3	4	4	1.3	8	9	1.3
Cerebral infarction	1	1	0.3	2	2	0.7	3	3	0.5
Cerebrovascular accident	2	2	0.6	1	1	0.3	3	3	0.5
Aphasia	1	1	0.3	0	0	0	1	1	0.2
Haemorrhagic stroke	0	0	0	1	1	0.3	1	1	0.2
Ischaemic stroke	1	1	0.3	0	0	0	1	1	0.2
Cardiac disorders	2	2	0.6	3	4	1.0	5	6	0.8
Cardiac failure	1	1	0.3	2	2	0.7	3	3	0.5
Angina pectoris	1	1	0.3	0	0	0	1	1	0.2
Cardio-respiratory arrest	0	0	0	1	1	0.3	1	1	0.2
Coronary artery disease	0	0	0	1	1	0.3	1	1	0.2
Gastrointestinal disorders	2	2	0.6	3	3	1.0	5	5	0.8
Gastrointestinal haemorrhage	2	2	0.6	0	0	0	2	2	0.3
Duodenal ulcer	0	0	0	1	1	0.3	1	1	0.2
Large intestine polyp	0	0	0	1	1	0.3	1	1	0.2
Rectal polyp	0	0	0	1	1	0.3	1	1	0.2
Eye disorders	3	3	1.0	0	0	0	3	3	0.5
Retinal haemorrhage	2	2	0.6	0	0	0	2	2	0.3
Retinal depigmentation	1	1	0.3	0	0	0	1	1	0.2
Hepatobiliary disorders	3	3	1.0	0	0	0	3	3	0.5
Cholelithiasis	2	2	0.6	0	0	0	2	2	0.3
Drug-induced liver injury	1	1	0.3	0	0	0	1	1	0.2

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Injury, poisoning and procedural complications	3	4	1.0	0	0	0	3	4	0.5
Hand fracture	1	1	0.3	0	0	0	1	1	0.2
Hip fracture	1	1	0.3	0	0	0	1	1	0.2
Pelvic fracture	1	2	0.3	0	0	0	1	2	0.2
Respiratory, thoracic and mediastinal disorders	1	1	0.3	2	2	0.7	3	3	0.5
Respiratory failure	1	1	0.3	1	1	0.3	2	2	0.3
Obstructive airways disorder	0	0	0	1	1	0.3	1	1	0.2
Blood and lymphatic system disorders	1	1	0.3	1	1	0.3	2	2	0.3
Anaemia	1	1	0.3	1	1	0.3	2	2	0.3
Musculoskeletal and connective tissue disorders	1	1	0.3	1	1	0.3	2	2	0.3
Intervertebral disc protrusion	0	0	0	1	1	0.3	1	1	0.2
Spinal stenosis	1	1	0.3	0	0	0	1	1	0.2
Ear and labyrinth disorders	0	0	0	1	1	0.3	1	1	0.2
Vertigo	0	0	0	1	1	0.3	1	1	0.2
General disorders and administration site conditions	1	1	0.3	0	0	0	1	1	0.2
Multiple organ dysfunction syndrome	1	1	0.3	0	0	0	1	1	0.2
Skin and subcutaneous tissue disorders	1	1	0.3	0	0	0	1	1	0.2
Psoriasis	1	1	0.3	0	0	0	1	1	0.2
Uncoded	0	0	0	1	1	0.3	1	1	0.2
Uncoded	0	0	0	1	1	0.3	1	1	0.2
Vascular disorders	1	1	0.3	0	0	0	1	1	0.2
Arteriosclerosis	1	1	0.3	0	0	0	1	1	0.2

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.
Source: Table 14.3.1.6.1

One SAE reported for the Lucentis arm is referred to as "uncoded". The applicant clarified that the SAE reported for subject as "uncoded" in the interim CSR was finally codes as cholangitis acute in the final updated CSR.

Causality assessment

Furthermore, only 3 of those 72 reported serious TEAE were considered related to study treatment or protocol-required procedures: 1 event of retinal haemorrhage in 1 subject in the Rimmyrah group that was related to study treatment, 1 event of endophthalmitis in 1 subject in the Rimmyrah group that was unrelated to study treatment but related to protocol-required procedures, and 1 event of endophthalmitis in 1 subject in the Lucentis group that was related to both study treatment and protocol-required procedures.

A tabulated summary of SAE has been provided, as requested. No notable differences between the treatment arms could be detected.

In addition, summarized information has been provided whether patients experiencing SAE, especially those SAE considered related to the study drug, did fully recover.

Ocular SAE

With regard to SAE in the study eye, a total of 5 subjects (0.8%) experienced 5 serious TEAE (4 events in 4 subjects in the Rimmyrah group [1.3%] and 1 event in 1 subject in the Lucentis group [0.3%]). In the Rimmyrah group, 2 subjects experienced serious TEAE of retinal haemorrhage, and 1 subject each experienced a serious TEAE of retinal depigmentation and endophthalmitis. One subject in the Lucentis group experienced a serious TEAE of endophthalmitis.

When analyzed for the subgroup "Region - Europe", ocular SAE in the study eye were reported from 2 subjects (1.1%) in the Rimmyrah arm and from 1 subject (0.5%) in the EU-Lucentis arm. The most frequently reported ocular SAE in the study eye for the European subgroup by PT were Retinal hemorrhage (QL1205: n=2 vs. Lucentis: n=0) and Endophthalmitis (QL1205: n=0 vs. Lucentis: n=1).

There were numerically higher incidences of overall SAE observed in the Rimmyrah arm than in the Lucentis arm (10.8% vs 6.6%) in the region Europe. This numerical imbalance was mainly triggered by non-ocular SAE which occurred in 9.7% of subjects in the Rimmyrah arm compared to 6.6% in the Lucentis arm.

In the Rimmyrah arm, 5 events of COVID-19 and 4 events of pneumonia were reported for the region Europe, compared to only 2 events of pneumonia in the Lucentis arm (and no COVID-19 events). Also, more events from the SOC Nervous system disorders were observed in the Rimmyrah arm (6 events) than in the Lucentis arm (2 events).

However, for region Europe, only 2 SAE in the Rimmyrah arm (retinal haemorrhage, vitreous haemorrhage) and 1 SAE in the Lucentis arm (endophthalmitis) were judged treatment-related. They all occurred in the study eye. All other SAE were judged unrelated to study treatment.

From Rapporteur´s point of view, there is no cause for concern with regard to the numerical imbalance in the overall (non-ocular) SAE incidence between the study arms seen for the region Europe, given the fact that this imbalance was not observed for SAE judged related to study treatment.

<u>In the fellow eye,</u> no serious TEAE occurred.

<u>Non-ocular SAE</u>

Overall 43 subjects [7.0%] experienced 67 non-ocular SAE. The incidence of non-ocular SAE was overall comparable between the treatment arms: 24 subjects in the Rimmyrah group [7.8%] with 40 events and 19 subjects in the Lucentis group [6.2%] with 27 events.

Serious non-ocular TEAE that occurred in ≥0.5% of subjects overall included COVID-19 (QL1205: 1.6%, Lucentis: 0), pneumonia (QL1205: 1.3%, Lucentis: 0.3%), cerebral infarction (QL1205: 0.3%, Lucentis: 0.7%), cerebrovascular accident (QL1205: 0.6%, Lucentis: 0.3%), and cardiac failure (QL1205: 0.3%, Lucentis: 0.7%).

All these reported non-ocular SAE were judged unrelated to study treatment.

<u>Deaths</u>

Eight patients died during the course of the study until DCO for the Interim CSR; 5 patients were exposed to Rimmyrah, and 3 patients were exposed to Lucentis. The Investigators judged these fatal SAE as unrelated to study treatment or to protocol-required procedures.

Rimmyrah group:

Subject experienced severe TEAE of gastrointestinal hemorrhage, multiple organ dysfunction syndrome, and septic shock and died on the same day. The events were not considered to be related to study treatment or protocol-required procedures.

Subject experienced a severe TEAE of COVID-19 pneumonia and died approximately a week later. The event was not considered to be related to study treatment or protocol-required procedures.

Subject experienced severe TEAE of COVID-19, pneumonia viral, and respiratory failure and died. The events were not considered to be related to study treatment or protocol-required procedures.

Subject experienced a severe TEAE of ischaemic stroke and died a month later. The event was not considered to be related to study treatment or protocol-required procedures.

Subject experienced a severe TEAE of gastrointestinal haemorrhage on and died approximately 1 month later on. The event was not considered to be related to study treatment or protocol-required procedures.

Lucentis group:

Subject experienced severe TEAE of cardiac failure, cardio-respiratory arrest, and obstructive airways disorder and died on the same day. The events were not considered to be related to study treatment or protocol-required procedures.

Subject experienced a moderate TEAE of anaemia and a severe TEAE of gastric cancer and died. The events were not considered to be related to study treatment or protocol-required procedures.

Subject experienced a severe TEAE of cardiac failure on and died on the same day. The event was not considered to be related to study treatment or protocol-required procedures.

Complete case reports are included in the documentation and do not give any reason for concern.

Supportive Phase 1 study QL1205-001

In the supportive Phase 1 study in Chinese patients, a total of 2 (8.7%) subjects from the Rimmyrah arm reported 2 SAE (Arrhythmia, Pancreatic carcinoma) during the study, one leading to death of the respective subject (Pancreatic carcinoma). Both SAE were judged not related to study treatment.

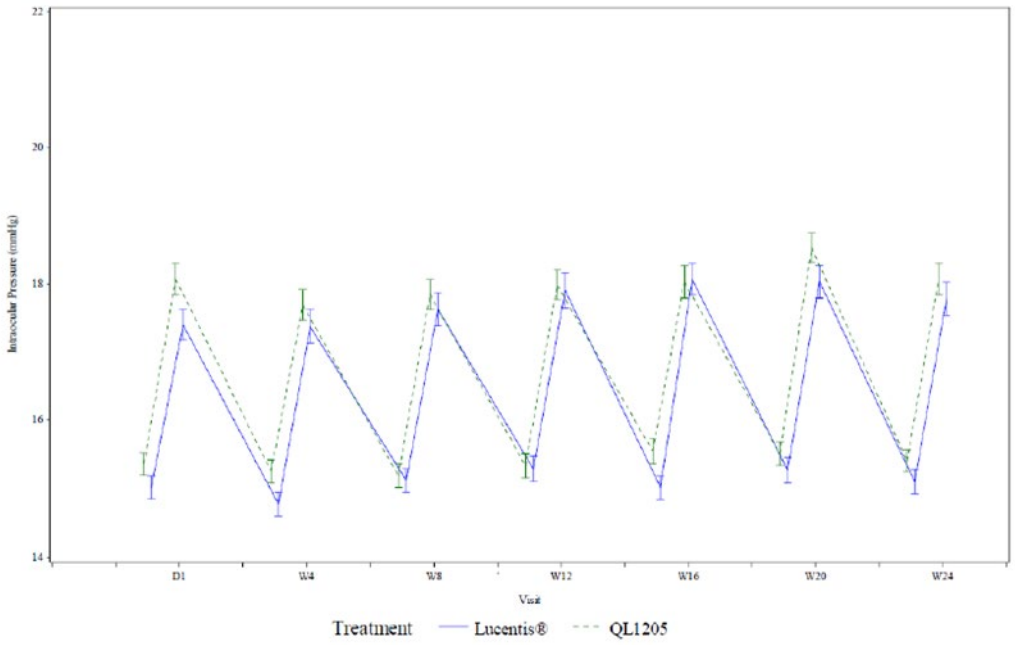
2.4.9.4. Laboratory findings

Pivotal Phase 3 study QL1205-002

The clinical Phase 3 study showed comparable patterns of safety laboratory, vital signs and ophthalmological examination assessments between QL1205- and Lucentis-treated patients. The vast majority of reported laboratory results were within normal ranges, or not clinically significantly below or above normal ranges. No clinically meaningful laboratory abnormalities were identified which could not be explained by a geriatric patient population.

No notable results were observed from vital sign assessments, physical examination, slit-lamp examination, dilated fundus examination, and color fundus photography. IOP increased in both groups 30 minutes post injection at all time points, however, no notable differences between the groups were observed.

Figure 8. Mean (± Standard Error) Intraocular Pressure in the Study Eye



Overall, the results up to Week 24 do not indicate any relevant differences between the two treatment arms.

Supportive Phase 1 study QL1205-001

With regard to laboratory values, vital signs and other study examinations, no significant abnormalities were reported.

2.4.9.5. In vitro biomarker test for patient selection for safety

N/A

2.4.9.6. Safety in special populations

N/A

2.4.9.7. Immunological events

Please refer to Overview Section 3.3.1.2 "Pharmacodynamics" for immunogenicity results and assessment.

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

N/A

2.4.9.9. Discontinuation due to adverse events

Pivotal Phase 3 study QL1205-002

Up to the DCO of January 2022, a total of 13 patients (QL1205: n= 5 with 7 events, Lucentis: n=8 with 9 events) permanently discontinued study treatment due to 16 TEAE. Of those TEAE leading to treatment discontinuation, 2 events in 2 subjects in the Rimmyrah arm and 4 events in 3 subjects in

the Lucentis arm occurred in the study eye. All other TEAE that led to treatment discontinuation were non-ocular ones. None of the TEAE leading to treatment discontinuation occurred in the fellow eye.

The frequencies and types of TEAE leading to withdrawal of study drug until DCO were balanced between both treatment groups, and no clinically relevant differences were identified.

Table 54. Treatment-Emergent Adverse Events Leading to Treatment Discontinuations by System Organ Class and Preferred Term – All – Safety Set

SOC PT	QL1205 (N=309)			Lucentis (N=307)			Overall (N=616)		
	n	e	%	n	e	%	n	e	%
Number of subjects with at least 1 TEAE	5	7	1.6	8	9	2.6	13	16	2.1
Eye disorders	2	2	0.6	2	3	0.7	4	5	0.6
Detachment of retinal pigment epithelium	0	0	0	1	1	0.3	1	1	0.2
Macular degeneration	1	1	0.3	0	0	0	1	1	0.2
Macular oedema	0	0	0	1	1	0.3	1	1	0.2
Retinal depigmentation	1	1	0.3	0	0	0	1	1	0.2
Retinal haemorrhage	0	0	0	1	1	0.3	1	1	0.2
Infections and infestations	2	3	0.6	1	1	0.3	3	4	0.5
COVID-19	1	1	0.3	0	0	0	1	1	0.2
Dacryocystitis	0	0	0	1	1	0.3	1	1	0.2
Pneumonia	1	1	0.3	0	0	0	1	1	0.2
Pneumonia viral	1	1	0.3	0	0	0	1	1	0.2
Nervous system disorders	0	0	0	3	3	1.0	3	3	0.5
Cerebral infarction	0	0	0	1	1	0.3	1	1	0.2
Cerebrovascular accident	0	0	0	1	1	0.3	1	1	0.2
Haemorrhagic stroke	0	0	0	1	1	0.3	1	1	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	2	2	0.7	2	2	0.3
Breast cancer	0	0	0	1	1	0.3	1	1	0.2
Non-Hodgkin's lymphoma	0	0	0	1	1	0.3	1	1	0.2
Psychiatric disorders	1	1	0.3	0	0	0	1	1	0.2
Fear of injection	1	1	0.3	0	0	0	1	1	0.2
Respiratory, thoracic and mediastinal disorders	1	1	0.3	0	0	0	1	1	0.2
Respiratory failure	1	1	0.3	0	0	0	1	1	0.2

Abbreviations: e, number of events; N, number of subjects; n, number of subjects in the specified category; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.
Source: Table 14.3.1.7.1

According to the applicant, most of the TEAE that led to treatment discontinuations of Rimmyrah were unrelated to study treatment or protocol-required procedures except for 1 moderate event of macular degeneration (left eye) in 1 subject in the Rimmyrah group that was considered related to study treatment. In the Lucentis arm, of the 8 subjects with 9 events that led to treatment discontinuations, 3 events in 2 subjects were considered related to study treatment: moderate macular oedema and retinal haemorrhage (both in the right eye) in 1 subject and moderate detachment of retinal pigment epithelium in 1 subject.

An updated analysis of treatment discontinuation due to adverse events has been provided by the applicant has been provided, as requested.

Overall, 5 subjects (1.6%) in the Rimmyrah group experienced 7 events leading to treatment discontinuation, while 8 subjects (2.6%) in the Lucentis group experienced 9 events.

Most of the TEAE that led to treatment discontinuation were unrelated to study treatment or protocol-required procedures except for 1 moderate event of macular degeneration (in the study eye) in 1 subject in the Rimmyrah group that was considered related to study treatment.

In the Lucentis group, 3 events in 2 subjects were considered related to study treatment: moderate macular oedema and retinal haemorrhage (both in the study eye) in 1 subject and moderate detachment of retinal pigment epithelium (in the study eye) in 1 subject.

Serious adverse events leading to treatment discontinuation were experienced by 3 subjects (1.0%) in the Rimmyrah arm (5 SAE) and by 3 subjects (1.0%) in the Lucentis arm (3 SAE).

The serious adverse events leading to treatment discontinuation reported from the Rimmyrah arm were (by PT): COVID-19, pneumonia, pneumonia viral, retinal depigmentation, and respiratory failure.

The SAE reported from the Lucentis arm were (by PT): Cerebral infarction, cerebrovascular accident, and haemorrhagic stroke.

With regard to TEAE as well as SAE leading to treatment discontinuation, no notable imbalances, which might question safety similarity between treatment arms, were identified.

Supportive Phase 1 study QL1205-001

A total of 46 (95.8%) subjects completed the study. Two subjects, 1 subject from the Rimmyrah group and 1 from the Lucentis group, withdrew from the study prematurely. The reason for withdrawal was SAE for the subject in the Rimmyrah group, and the reason for withdrawal for the subject in the Lucentis group was that Investigator recommended withdrawal from the trial in consideration of subject safety.

2.4.9.10. Post marketing experience

This section is not applicable, since Rimmyrah (QL1205) has not been approved or marketed yet in any country worldwide. There is wide overall clinical experience with ranibizumab (Lucentis) in the approved therapeutic indications, and a positive efficacy and safety record has been established.

As it is a regulatory requirement of biotechnology-derived products to undertake post-marketing activities including routine pharmacovigilance activities, supplying a patient alert card (PAC) to record important safety information, as well as participation in patient registries, the reporting of additional safety and efficacy assessments in periodic safety update reports (PSURs) is defined in the Risk Management Plan (RMP) in accordance with EMA guidelines (EMA/CHMP/BMWP/403543/2010, EMEA/CHMP/BMWP/14327/2006).

2.4.10. Discussion on clinical safety

Two clinical studies were conducted to compare the safety profiles of Rimmyrah and Lucentis:

- The **pivotal Phase 3 study QL1205-002** was conducted in Europe, China and India, including a total of 616 subjects diagnosed with nAMD who received 0.5mg ranibizumab (either Rimmyrah or EU-Lucentis; 1:1 randomized) by IVT injection once every 4 weeks with 13 consecutive doses.
- In addition, a **supportive Phase 1 study (QL1205-001)** was conducted in China including 48 AMD patients who received either Rimmyrah or Lucentis once every 4 weeks for 3 consecutive doses.

Key safety information was derived from the Phase 3 study QL1205-002, supported by safety and tolerability data from the Phase 1 study.

Neovascular AMD is considered a sufficiently sensitive population to investigate clinical biosimilarity in terms of safety, as there is comparability for ranibizumab across indications with regard to target receptor, mode of action and safety across authorised indications, i.e., DME, RVO, CNV and PDR. In addition, immunogenicity of ranibizumab was reported to be overall low across indications (up to 9%).

The Q4W administration of the study drugs is in accordance with the anticipated posology in patients with the highest treatment need. From a safety perspective, a monthly schedule is most sensitive, as higher exposure levels can be expected in comparison with a treat and extend regimen, and is thus supported.

Study duration of the pivotal Phase 3 study was 12 months, with 13 monthly injections. A study duration of 12 months is considered a relevant time period to assess safety and immunogenicity in a biosimilarity exercise.

With dossier submission, only 24 weeks safety data from the pivotal Phase 3 study were available for review. However, the final 52 weeks safety data have been submitted during the procedure.

In this study, safety was assessed based on the occurrence of adverse events (AEs) and serious adverse events (SAE) categorised by SOC and PT and coded by MedDRA as well as any changes in vital signs, laboratory assessment, and immunogenicity. The Safety Set (SAF) in each study included any individuals who received at least one or more dose of IMP.

Per treatment arm, 309 (QL1205) and 307 (EU-Lucentis) patients were included in the SAF of the pivotal Phase 3 study, respectively. This was due to the fact that one subject was administered an incorrect IMP kit at Day 1 visit because of site error (i.e. randomized to Lucentis but received QL1205). This subject was subsequently discontinued from study treatment because of an SAE of stroke and did not receive any more doses (i.e. only received 1 dose of QL1205).

Originally, the applicant applied for the same adult and paediatric indications as approved for the originator, Lucentis; including the ROP indication in preterm infants. However, no suitable device for administration to the paediatric population was presented by the applicant. This triggered a multidisciplinary MO during the first assessment round.

With his response to the D120 LoQ, the applicant decided to withdraw the claim for the ROP indication. Thus, only the Lucentis-approved adult indications are applied for.

Comparative safety data from the **pivotal Phase 3 study QL1205-002** involved 616 randomized patients (QL1205: n=309, EU-Lucentis n=307), most of whom (n=596, 96.4%) completed the study treatment up to Week 24.

Overall, demographic and baseline characteristics were balanced between treatment arms, and the population that was investigated was sufficiently sensitive for the evaluation of similarity from a safety (and efficacy) perspective.

Treatment compliance up to Week 8 was 97.4% in the Rimmyrah group and 98.5% in the Lucentis group. Compliance up to Week 24 was 99.01% in the Rimmyrah group and 99.27% in the Lucentis group. There were no notable differences in treatment compliance between the 2 groups.

Similar amounts of study drug were administered to patients in both treatment arms, no notable differences were observed.

The main reason for not completing the study treatment up to Week 24 was subject withdrawal of consent (9 subjects, 1.5%), followed by AE and other reasons (5 subjects each, 0.8%). Of the 616 randomised subjects, 44 subjects (7.1%) discontinued the study prematurely as of the data cut-off of 27 Jan 2022 (n=17 in the Rimmyrah arm, n=27 in the Lucentis arm), mainly because of withdrawal of consent (18 subjects, 2.9%), followed by AE and other reasons (10 subjects each, 1.6%).

TEAE by SOC/PT

The most commonly affected SOCs in both treatment groups in the SAF of the pivotal Phase 3 study were Eye disorders, Infections and infestations, and Investigations. Overall, the SOC Eye disorders was the most commonly affected SOC for both treatment arms in the SAF (QL1205: 37.2% of patients with 173 events; Lucentis: 35.2% of patients with 175 events). The most commonly affected PTs in this SOC were Neovascular age-related macular degeneration (QL1205: 4.5%; Lucentis: 3.3%), Visual acuity reduced (QL1205: 3.2%; Lucentis: 3.9%), and Conjunctival haemorrhage (QL1205: 3.6%; Lucentis: 2.6%).

Other commonly affected PTs were Hypertension from SOC Infections and Infestations (QL1205: 5.5%; Lucentis: 7.5%) and IOP increased from SOC Investigations (QL1205: 3.9%; Lucentis: 2.6%).

Ocular TEAE in study eye

Frequency of ocular TEAE in the study were overall comparable between both treatment groups in the pivotal Phase 3 study. Overall, 161 events occurred in 104 subjects in the Rimmyrah group (33.7%) compared to 162 events in 99 subjects in the Lucentis group (32.2%).

The most frequently occurring TEAE by SOC were Eye disorders (QL1205: 29.8%, Lucentis: 28.7%), Investigations (QL1205: 3.6%, Lucentis: 2.6%), and Infections and infestations (QL1205: 2.3%, Lucentis: 2.6%). The most frequently occurring TEAE by PT were Conjunctival haemorrhage (QL1205: 3.6%, Lucentis: 2.6%), IOP increased (QL1205: 3.6%, Lucentis: 2.6%), and Macular fibrosis (QL1205: 2.6%, Lucentis: 2.9%).

When analyzed for the subgroup "Region - Europe", ocular TEAE in the study eye were reported from 64 subjects (34.6%) in the Rimmyrah arm and from 63 subjects (34.6%) in the EU-Lucentis arm. The most frequently reported ocular TEAE in the study eye for the European subgroup by PT were macular fibrosis (QL1205: 4.3% vs. Lucentis: 4.9%) and visual acuity reduced (4.9% vs 3.8%).

An analysis of TEAE by region has been provided for ocular TEAE in the study eye only (Tables 14.3.1.8 and 14.3.1.9 in the Interim CSR).

According to the Lucentis SmPC, the most frequently reported ocular adverse reactions following Lucentis injection are: eye pain, ocular hyperaemia, increased intraocular pressure, vitreous detachment, retinal haemorrhage, visual disturbance, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus. However, in the pivotal Phase 3 study, macular fibrosis was one of the most frequently reported TEAE by PT with incidences of 2.6% (n=8 events in the Rimmyrah arm) and 2.9% (n=9 events in the Lucentis arm). The applicant was requested to discuss the imbalance between the ocular safety profile outlined in the Lucentis SmPC and the reported ocular TEAE by PT in the pivotal study.

The applicant stressed that the formation of subretinal/ macular fibrosis occurs in the natural course of the wAMD disease as a wound healing response to CNV. This is acknowledged. It is well-known that anti-VEGF therapy can only delay the formation of fibrosis, but does not necessarily prevent it. Thus, typically subretinal fibrosis is not per se an adverse event, but part of the natural course of the wAMD disease progression.

Ocular TEAE in fellow eye

A total of 113 TEAE occurred in the fellow eye for 88 subjects (14.3%) in the pivotal Phase 3 study, with 54 events in 45 subjects in the Rimmyrah group (14.6%) and 59 events in 43 subjects in the Lucentis group (14.0%). Most TEAE in the fellow eye fall under the SOC of Eye disorders (QL1205: 13.9%, Lucentis: 12.4%). TEAE in the fellow eye that occurred in ≥1.0% of subjects were Neovascular

age-related macular degeneration (QL1205: 4.2%, Lucentis: 3.3%), Visual acuity reduced (QL1205: 0.3%, Lucentis: 2.3%), and Dry eye (QL1205: 1.6%, Lucentis: 0.3%).

Non-ocular TEAE

Frequencies of non-ocular (i.e. systemic) TEAE in the pivotal Phase 3 study were overall comparable between both treatment groups in the pivotal Phase 3 study, and no clinically relevant differences were identified. Overall, 458 events occurred in 172 subjects in the Rimmyrah group (55.7%) compared to 414 events in 165 subjects in the Lucentis group (53.7%).

Injection site reactions

Frequencies of injection site reactions were overall comparable between the study arms in the pivotal Phase 3 study: 43 events occurred in 35 subjects in the Rimmyrah group (11.3%), whereas 63 events occurred in 41 subjects in the Lucentis group (13.4%).

Injection site reactions which occurred in ≥1.0% of subjects included Conjunctival haemorrhage (QL1205: 3.2%, Lucentis: 2.3%), Foreign body sensation in eyes (QL1205: 1.6%, Lucentis: 2.3%), and IOP increased (QL1205: 2.3%, Lucentis: 1.6%).

All injections site reactions occurred in the study eye, except for 2 events that occurred in the fellow eye in 2 subjects in the Lucentis group: Foreign body sensation in eyes and an uncoded event – noted to be an event of binocular dry eye.

TEAE related to study drug

Overall, only a small number of TEAE was considered to be study-drug related in the pivotal Phase 3 study: A total of 36 subjects (5.8%) experienced 54 treatment-related TEAE, with comparable numbers for both treatment arms (QL1205: 18 events in 15 subjects [4.9%]; Lucentis: 36 events in 21 subjects [6.8%]). Most treatment-related TEAE were under the SOC of Eye disorders (QL1205: 3.2%, Lucentis: 4.9%) and Investigations (QL1205: 1.6%, Lucentis: 1.3%).

Overall, 34 subjects (5.5%) experienced 45 treatment-related TEAE in the study eye, with comparable frequencies for both treatment arms (QL1205: 17 events in 14 subjects [4.5%]; Lucentis: 28 events in 20 subjects [6.5%]). Most treatment-related TEAE in the study eye were under the SOC of Eye disorders (QL1205: 3.2%, Lucentis: 4.9%) and Investigations (QL1205: 1.3%, Lucentis: 1.3%). All treatment-related TEAE in the study eye occurred in <1.0% of subjects, except for IOP increased (1.3% in both treatment arms).

One subject in the Rimmyrah arm (0.3%) experienced 2 treatment-related TEAE in the fellow eye: dry eye and eye pruritus.

With regard to treatment-related non-ocular TEAE, overall 5 subjects experienced 7 events. Frequencies were balanced between treatment arms with 3 events (Hypertensive heart disease, Vertigo, Blood glucose increased) in 3 subjects (1.0%) in the Rimmyrah arm and 4 events (Upper respiratory tract infection [2 events], Osteitis, and Insomnia) in 2 subjects (0.7%) in the Lucentis arm.

TEAE related to protocol-required procedures

All TEAE with a reasonable causal relationship to any protocol-required procedure were classified in this category. Numerically higher numbers of TEAE related to protocol-required procedures were observed in the Lucentis arm (59 events in 41 subjects [13.4%], compared to 42 events in 33 subjects in the Rimmyrah arm [10.7%]).

With regard to TEAE in the study eye related to protocol-required procedures, the frequencies were overall comparable with 41 events in 32 subjects in the Rimmyrah group (10.4%)] and 53 events in 36 subjects in the Lucentis group (11.7%). Most TEAE in the study eye related to protocol-required

procedures were under the SOC of Eye disorders (QL1205: 7.4%, Lucentis: 9.1%) and Investigations (QL1205: 2.9%, Lucentis: 1.6%).

TEAE in the fellow-eye related to protocol-required procedures were rare and comparable between treatment arms (0.6% in both study arms).

Overall, 5 subjects (0.8%) experienced 6 non-ocular TEAE related to protocol-required procedures (1 event of Vertigo in 1 subject in the Rimmyrah group [0.3%] and 5 events (Nausea [2 events], Retching, Back pain, Dermatitis) in 4 subjects in the Lucentis group [1.3%]).

TEAE by severity

Overall, most TEAE reported in the pivotal Phase 3 study were of mild (QL1205: 45.6%; Lucentis: 41.0%) or moderate intensity (QL1205: 18.8%; Lucentis: 22.8%); only a few severe TEAE were reported (QL1205: 7.4%; Lucentis: 5.9%).

With regard to ocular TEAE in the study eye, most TEAE were mild (QL1205: 25.9%; Lucentis: 25.7%) or moderate (QL1205: 5.2%; Lucentis: 7.5%). Severe TEAE in the study eye occurred in 1.3% of subjects in both groups.

In the fellow eye, most TEAE were mild (QL1205: 9.1%, Lucentis: 6.5%) or moderate (QL1205: 5.2%, Lucentis: 7.5%). A severe TEAE of cataract in the fellow eye occurred in 1 subject in the Rimmyrah group (0.3%).

Most non-ocular TEAE were mild (QL1205: 36.2%, Lucentis: 34.2%) or moderate (QL1205: 13.6%, Lucentis: 15.0%). Severe non-ocular TEAE occurred in 5.8% of subjects in the Rimmyrah group and in 4.6% of subjects in the Lucentis group

SAE

Frequencies of SAE reported up to the interim cut-off date of 27 January 2022 were overall low in the pivotal Phase 3 study: A total of 47 patients (7.6%) experienced 72 SAE. However, a numerically higher number of patients (n=28 [9.1%] with 44 events) in the Rimmyrah group experienced a serious TEAE than in the Lucentis group (n=19 [6.2%] with 28 events). Importantly, all serious TEAE occurred in <1% of subjects overall, and most were non-ocular events.

One SAE reported for the Lucentis arm is referred to as "uncoded". The applicant clarified that the SAE reported for subject as "uncoded" in the interim CSR was finally codes as cholangitis acute in the final updated CSR.

SAE related to study drug

Furthermore, only 3 of those 72 reported serious TEAE were considered related to study treatment or protocol-required procedures: 1 event of retinal haemorrhage in 1 subject in the Rimmyrah group that was related to study treatment, 1 event of endophthalmitis in 1 subject in the Rimmyrah group that was unrelated to study treatment but related to protocol-required procedures, and 1 event of endophthalmitis in 1 subject in the Lucentis group that was related to both study treatment and protocol-required procedures.

Ocular SAE

With regard to SAE in the study eye, a total of 5 subjects (0.8%) experienced 5 serious TEAE (4 events in 4 subjects in the Rimmyrah group [1.3%] and 1 event in 1 subject in the Lucentis group [0.3%]). In the Rimmyrah group, 2 subjects experienced serious TEAE of retinal haemorrhage, and 1 subject each experienced a serious TEAE of retinal depigmentation and endophthalmitis. One subject in the Lucentis group experienced a serious TEAE of endophthalmitis.

When analyzed for the subgroup "Region - Europe", ocular SAE in the study eye were reported from 2 subjects (1.1%) in the Rimmyrah arm and from 1 subject (0.5%) in the EU-Lucentis arm. The most frequently reported ocular SAE in the study eye for the European subgroup by PT were Retinal hemorrhage (QL1205: n=2 vs. Lucentis: n=0) and Endophthalmitis (QL1205: n=0 vs. Lucentis: n=1).

There were numerically higher incidences of overall SAE observed in the Rimmyrah arm than in the Lucentis arm (10.8% vs 6.6%) in the region Europe. This numerical imbalance was mainly triggered by non-ocular SAE which occurred in 9.7% of subjects in the Rimmyrah arm compared to 6.6% in the Lucentis arm.

In the Rimmyrah arm, 5 events of COVID-19 and 4 events of pneumonia were reported for the region Europe, compared to only 2 events of pneumonia in the Lucentis arm (and no COVID-19 events). Also, more events from the SOC Nervous system disorders were observed in the Rimmyrah arm (6 events) than in the Lucentis arm (2 events).

However, for region Europe, only 2 SAE in the Rimmyrah arm (retinal haemorrhage, vitreous haemorrhage) and 1 SAE in the Lucentis arm (endophthalmitis) were judged treatment-related. They all occurred in the study eye. All other SAE were judged unrelated to study treatment.

From CHMP point of view, there is no cause for concern with regard to the numerical imbalance in the overall (non-ocular) SAE incidence between the study arms seen for the region Europe, given the fact that this imbalance was not observed for SAE judged related to study treatment.

In the fellow eye, no serious TEAE occurred.

Non-ocular SAE

Overall 43 subjects [7.0%] experienced 67 non-ocular SAE. The incidence of non-ocular SAE was overall comparable between the treatment arms: 24 subjects in the Rimmyrah group [7.8%] with 40 events and 19 subjects in the Lucentis group [6.2%] with 27 events.

Serious non-ocular TEAE that occurred in ≥0.5% of subjects overall included COVID-19 (QL1205: 1.6%, Lucentis: 0), pneumonia (QL1205: 1.3%, Lucentis: 0.3%), cerebral infarction (QL1205: 0.3%, Lucentis: 0.7%), cerebrovascular accident (QL1205: 0.6%, Lucentis: 0.3%), and cardiac failure (QL1205: 0.3%, Lucentis: 0.7%).

All these reported non-ocular SAE were judged unrelated to study treatment.

Deaths

Eight patients died during the course of the study until DCO for the Interim CSR; 5 patients were exposed to Rimmyrah, and 3 patients were exposed to Lucentis. The Investigators judged these fatal SAE as unrelated to study treatment or to protocol-required procedures.

The applicant was requested to provide details of the deaths of patients from the Rimmyrah group. Specifically, the correlation between the timing of the product administration and the occurrence of adverse events and deaths should be discussed. Detailed information on the deaths of those patients has been provided. According to these data, the deaths are not related to the study drug.

Overall, based on the safety data presented from the pivotal QL1205-002 study, the safety profile of Rimmyrah can be considered similar to that of Lucentis.

2.4.11. Conclusions on the clinical safety

Originally, the applicant applied for the same adult and paediatric indications as approved for the originator, Lucentis; including the ROP indication in preterm infants. However, no suitable device for

administration to the paediatric population was presented by the applicant. With his response to the D120 LoQ, the applicant decided to withdraw the claim for the ROP indication. Thus, only the Lucentis-approved adult indications are ultimately applied for.

With this submission, initially only preliminary safety data until DCO (27 January 2022) were provided. The final data set was pending at the time point of dossier submission. However, 52 weeks safety data have been submitted with the responses to the D120 LoQ, substantiating safety similarity between biosimilar and originator.

No notable differences or imbalances between Rimmyrah and Lucentis have been observed, and no new safety signals were detected.

2.5. Risk Management Plan

2.5.1. Safety concerns

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

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities are deemed necessary.

2.5.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infectious endophthalmitis	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and 6.6.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PIL sections 2, 3 and 4. Restricted medical prescription Additional risk minimisation measures: • Educational plan for adult patients.	Additional pharmacovigilance activities: None.
Intraocular inflammation	Routine risk minimisation measures: SmPC sections 4.3 and 4.4. PIL sections 2 and 4. Restricted medical prescription. Additional risk minimisation measures: Educational plan 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 4.4 and 4.8. PIL sections 2 and 4. Restricted medical prescription. Additional risk minimisation measures: Educational plan 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 4.4, 4.8 and 4.9. PIL sections 2 and 4. Restricted medical prescription. Additional risk minimisation measures: Educational plan for adult patients.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

2.5.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. 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.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Rimmyrah (also referred to as QL1205) has been developed as a biosimilar to the reference product Lucentis. The administration route (intravitreal) and posology are in accordance with the reference product as described in the Lucentis SmPC.

The marketing authorization has been asked for the following indications in adult patients:

- 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

For the biosimilarity exercise, the quality attributes of the reference medicinal product in terms of its physicochemical and functional properties were characterized. The identified quality attributes were ranked according to (a) their risk to potentially impact efficacy, PK/PD, immunogenicity, safety, and (b) the degree of uncertainty surrounding a certain quality attribute. Assignment of statistical analysis

and corresponding similarity ranges for the physicochemical and biological quality attributes was based on the criticality risk ranking of the quality attributes.

Overall, sample selection and sample size are considered adequate.

A large panel of standard and state-of-the-art methods has been used to characterize and compare the most relevant physicochemical and biological quality attributes of the ranibizumab molecule. Analytical methods have been qualified or validated.

To support the known mechanism of action, binding to VEGF and inhibition of cell proliferation was assessed by functional and binding assays in the scope of the biosimilarity exercise. Assays include cell-based bioassays (VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A189), a binding assay (VEGF-A165), a cell migration assay (VEGF-A165) and the determination of binding affinities towards VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A189 by Surface Plasmon Resonance (SPR).

Furthermore, primary structure, higher order structure, size variants, charge variants, hydrophobicity, protein concentration and particulate contamination were assessed using a variety of methods.

Overall, the applicant followed relevant guidelines and performed an extensive biosimilarity exercise using sensitive orthogonal state-of-the-art analytical methods. All relevant quality attributes were addressed.

Non-clinical data

The non-clinical comparability included several studies (pharmacodynamic, pharmacokinetic and toxicology) to support the biosimilarity of Rimmyrah to the reference medicinal product Lucentis. The provided in vitro study results show good comparability between Rimmyrah and EU-Lucentis in terms of binding characteristics pharmacological effects (inhibition of cell proliferation induced by VEGF-A). Additionally, the non-clinical program included in vivo studies in several species. According to the applicable Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) those studies are not considered necessary, given the good comparability between Rimmyrah and the reference medicinal product, and are discouraged. In general, these data are considered supportive in terms of this MAA, especially as the origin of the Lucentis batches used in the in vivo studies is not clearly stated.

In conclusion, there are no issues from the non-clinical package regarding the biosimilarity of Rimmyrah to EU-Lucentis.

Clinical data package

The clinical developmental program comprises a pivotal Phase 3 comparative efficacy and safety study in patients with nAMD (QL1205-002) and a supportive Phase 1 study to investigate preliminary safety in patients with nAMD (QL1205-001) conducted in China.

Clinical similarity with regard to **efficacy** was evaluated in study QL1205-002, a randomised, double-masked, parallel-group, multicentre Phase 3 study investigating efficacy, safety, PK, and immunogenicity of Rimmyrah versus EU-Lucentis in 616 subjects with nAMD subjects who were randomized 1:1 to receive 13 doses of either Rimmyrah or EU-Lucentis Q4W. Overall study duration was 52 weeks. A core efficacy analysis was performed on unmasked study data. After all subjects were randomised and all subjects had 6-month (i.e. 24 weeks) data available, an analysis of primary efficacy and secondary endpoints was performed. The aim of this efficacy analysis was to obtain results on the primary endpoint before completion of full follow-up for all subjects. Supportive data were obtained from the analyses of the final 52 week data set.

Clinical safety was investigated in both clinical studies, i.e. in the Phase 3 study QL1205-002 outlined above and in the Phase 1 study QL1205-001 conducted in 48 Chinese nAMD patients, who received 3

IVT injections of either Rimmyrah or EU-Lucentis every 4 weeks (study duration was 12 weeks). DCO for the submitted safety data of the Phase 3 study was 27 January 2022. Thus, the full set of safety and immunogenicity data has been submitted during the MA procedure.

The design of the pivotal clinical study QL1205-002 has been discussed during two EMA scientific advices. Most of the issues discussed during the advices were followed by the applicant.

3.2. Results supporting biosimilarity

Quality

In summary, the presented analytical data show similarity of the proposed biosimilar Rimmyrah and the reference medicinal product EU-Lucentis. The results of the structural and physicochemical properties showed that Rimmyrah are within the similarity range determined by tested EU-Lucentis lots – except for protein concentration. Quality attributes related to the mechanism of action of ranibizumab were similar. Biological activity by cell-based bioassays (HUVEC proliferation assay), binding ELISA, cell migration assay and binding affinity by Surface Plasmon Resonance (SPR) are within the similarity range of EU-Lucentis.

Non-clinical

The provided non-clinical data package show similar effect on PD (in vitro and in vivo), PK and toxicological parameters. It is noted that based on the good comparability data from the analytical biosimilarity studies the non-clinical in vivo would not have been requested in line with the staggered approach described in Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). Furthermore, the origin of the Lucentis batches used in these studies have not been stated. Nevertheless, the provided results do not raise concerns regarding the biosimilarity between Rimmyrah and Lucentis.

In conclusion, from the nonclinical point of view, no major differences were observed between Rimmyrah and the EU-sourced comparator.

Clinical

Pharmacokinetics:

The observed serum concentration was similar between Rimmyrah and Lucentis in study QL1205-002. The mean and median of serum concentrations were within the predicted range of Lucentis Cmax.

Pharmacodynamics:

As there is no obvious PD biomarker used in the pivotal phase 3 study QL1205-002 that could allow for a reasonable interpretation of the PD studies, PD relies on *in vitro* data and the human efficacy study.

Efficacy:

In the pivotal Phase 3 comparative efficacy study QL1205-002 in 616 nAMD patients, equivalence between Rimmyrah and EU-Lucentis was demonstrated for the primary efficacy endpoint, 'Change in BCVA from Baseline at Week 8', both in the ITT and in the PP population. The difference between the two treatment arms was -1.05 ETDRS letters [95%CI: -2.46; 0.36] for the ITT population; the two-sided 95% CI was entirely within the pre-defined equivalence margin of ± 3.49 letters. This was supported by the analysis in the PP population (difference of -0.85 letters, with a 95% CI of -2.29; 0.58) - whose results were consistent with the primary analysis.

Several functional and anatomical parameters were assessed as secondary efficacy endpoints, in order to support demonstration of similar efficacy between Rimmyrah and Lucentis. Overall, comparability of Rimmyrah to Lucentis was demonstrated for the secondary efficacy endpoints up to Week 52.

Safety:

An adequate safety database has been submitted, including safety data from the pivotal multicentric Phase 3 study (n=616 subjects [n=367 from Europe]; n=309 in Rimmyrah arm [n=185 from Europe] and n=307 in Lucentis arm [n=182 from Europe]) with a study duration of 52 weeks (13 IVT injections), as well as supportive safety data from a Chinese Phase 1 study in 48 subjects with a duration of 12 weeks (3 IVT injections).

No notable differences or imbalances between Rimmyrah and Lucentis have been observed, and no new safety signals were detected.

Immunogenicity:

The total number of patients treated with Rimmyrah and Lucentis with positive ADAs in blood serum were low and similar between both treatments. Based on the data provided the immunogenicity of Rimmyrah and a safety risk due to clinically relevant treatment-emergent ADAs is assessed to be low.

3.3. Uncertainties and limitations about biosimilarity

Quality

For protein concentration a similarity range of 9.3-10.2 was determined. For Rimmyrah, the protein concentration results of two batches are out of the aforementioned similarity range. Although the two batches of Rimmyrah did not fall within the current similarity range (9.3-10.2 mg/mL), they still meet the specification described in EU-Lucentis Certificate of Analysis and the proposed Rimmyrah release and stability acceptance criterion (9.0-11.0 mg/mL). All other physicochemical and biological attributes have been demonstrated to be similar. In addition, clinical trial results indicate that the safety and efficacy profiles or the two products are similar. Overall, the quality package supports the biosimilarity claim and there are no open issues.

Non-clinical

There are no issues from the non-clinical package regarding the biosimilarity of Rimmyrah to EU-Lucentis.

Clinical

Pharmacokinetics:

There are no remaining issues from the pharmacokinetic data regarding the biosimilarity of Rimmyrah to EU-Lucentis.

Pharmacodynamics:

The clinical evaluation of similarity for Rimmyrah is based on clinical endpoints used in study QL1205-002 rather than a PD endpoint which is judged acceptable since no obvious PD endpoint is known.

Efficacy:

There are no remaining uncertainties from the clinical efficacy data regarding similarity of Rimmyrah with Lucentis.

Safety:

There are no remaining uncertainties regarding safety.

Immunogenicity:

Based on the analyses of the main estimand for the BCVA at Week 8 by ADA result (positive/negative up to Week 8) in study QL1205-002, it appears that ADA positive patients in the Rimmyrah treatment group might have a loss of efficacy, so that a potential difference between the originator and biosimilar in ADA positive patients on the efficacy endpoint BCVA at Week 8 cannot be fully excluded so far. Nevertheless, it needs to be considered, that the total number of ADA positive patients was quite small in general. In addition, the number of treatment-induced ADAs was even smaller and more or less similar between both treatment groups. In addition, the frequency of NAb was quite low as well (≤2 subjects at any time point). Therefore, based on the data provided, since only one subject in the Rimmyrah group had a positive NAb result between day 1 and week 8, no treatment failure due to loss of therapeutical function of QL-1205 would actually be expected. Given the data provided, the safety risk due to clinically relevant treatment-emergent ADAs is estimated to be low, and there is no evidence that ADA status on PK and safety will negatively impact biosimilarity.

3.4. Discussion on biosimilarity

Overall, the design of the analytical similarity exercise is considered adequate.

The results of the analytical similarity exercise between Rimmyrah and EU-Lucentis demonstrate similarity for most of the attributes – except for protein concentration. Analytical differences observed between Rimmyrah and the reference product have been justified with regard to their potential impact on clinical efficacy and safety.

There are no issues from the non-clinical package regarding the biosimilarity of Rimmyrah to EU-Lucentis.

The pivotal comparative efficacy study in nAMD patients investigating Rimmyrah and EU-Lucentis was overall adequately designed, and the primary and secondary efficacy outcomes and similarity criteria are considered acceptable. Equivalence was demonstrated for the primary endpoint, the change from baseline in BCVA at Week 8 in the ITT population. This was supported by sensitivity analyses for the primary EP in the PP population, as well as by secondary efficacy endpoints reflecting functional and anatomical outcomes.

A sufficiently large number of patients was treated with either Rimmyrah or the originator product, Lucentis, in the pivotal Phase 3 study.

With the initial submission, only preliminary safety data until DCO (27 January 2022) were provided. However, the final 52 weeks safety data have submitted during the MAA procedure, and no safety concerns have been identified. The overall study duration of 52 weeks is also considered adequate.

Overall, a positive benefit risk balance can be concluded.

3.5. Extrapolation of safety and efficacy

Ranibizumab binds to VEGF-A to prevent binding to corresponding receptors, thereby suppressing neovascularization. The mode of action of ranibizumab is considered to be the same across all approved indications of Lucentis. The biological activities related to the mode of action have been comprehensively evaluated in the analytical similarity exercise.

Extrapolation to the other indications of the reference product applied for is considered acceptable.

3.6. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

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

Rimmyrah 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)

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **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.

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

- **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.

- **Additional risk minimisation measures**

Prior to launch of Rimmyrah in each EU Member State the MAH shall agree the final educational plan for adult patients with the National Competent Authority.

The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Rimmyrah is marketed, at launch and after launch all ophthalmological clinics where Rimmyrah is expected to be used are provided with an up-to-date patient information pack.

The patient information pack should be provided in both the form of patient information booklets and an audio-CD that contain following key elements:

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