15 September 2022
EMA/CHMP/795998/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ximluci

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/005617/0000

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
ADR	Adverse Drug Reaction
AE	Adverse Events
ALT/SGPT	Serum Glutamic-PyruvicTransaminase
AST/SGOT	Serum Glutamic-Oxaloacetic Transaminase
AMD	Age-Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BDRM	Blind Data Review Meeting
BSE	Bovine spongiform encephalitis
CAA	Comparative Analytical Assessment
CDR	Complementarity determining region
CEX	Cation exchange chromatography
CFT	Central Foveal Thickness
CI	Confidence Interval
cIEF	Capillary isoelectric focusing
CNV	Choroidal Neovascularization
CPP	Critical process parameter
CQA	Critical quality attribute
DME	Diabetic Macula Edema
DOE	Design of experiments
DP	Drug Product
DR	Diabetic Retinopathy
DS	Drug Substance
ELISA	Enzyme linked immunosorbent assay
EOPCB	End of production cell bank
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
Fab	antibody-binding fragment
FAS	Full Analysis Set
Fc	Fragment crystallisable region
FDA	US Food and Drug Administration
FMEA	Failure mode and effects analysis

GLP	Good Laboratory Practice
GMP	Good manufacturing practice
hcDNA	Host cell DNA
HCP	Host cell protein
HIC	Hydrophobic interaction chromatography
HMW	High molecular weight species
HPLC	High performance liquid chromatography
HUVEC	Human umbilical cord vein endothelial cells
IgG1	Immunoglobulin G1
IPC	In process control
ISR	Injection Site Reaction
IVT	Intravitreal
LIVCA	Limit of in vitro cell age
LMW	Low molecular weight species
LOD	Limit of detection
LOQ	Limit of quantitation
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MCNV	Myopic Choroidal Neovascularization
MMRM	Mixed Model for Repeated Measures
NAb	Neutralizing anti-drug antibody
NOR	Normal operating range
PACMP	Post approval change management protocol
PAR	Proven acceptable range
PD	Pharmacodynamics
PDE	Permitted daily exposure
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PP	Process parameter
PPIA	Process parameter influence assessment
PPQ	Process performance qualification
PRS	Primary reference standard

PT	Preferred Term
PV	Process validation
QC	Quality control
RGA	Reporter gene assay
RhuMAb	Recombinant Humanized IgG1 Kappa Isotype Monoclonal Antibody
ROP	Retinopathy of prematurity
RMP	Reference Medicinal Product
ROW§	Rest of World
RP-HPLC	Reversed phase HPLC
RPN	Risk priority number
RVO	Maculae Edema Following Retinal Vein Occlusion
SAE	Serious Adverse events
SCX-HPLC	Strong cation exchange chromatography
SE-HPLC	Size exclusion HPLC
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TFF	Tangential flow filtration
TSE	Transmissible spongiform encephalopathy
UF/DF	Ultrafiltration/Diafiltration
US	United States
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
wAMD	Neovascular (wet) Age-Related Macular Degeneration
WCB	Working cell bank
WRS	Working reference standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant STADA Arzneimittel AG submitted on 9 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Ximluci, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Ximluci 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 non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- 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.

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**
23 March 2017	EMEA/H/SA/3522/1/2017/SME/III	Dr Jens Reinhardt and Prof Andrea Laslop
31 May 2018	EMEA/H/SA/3522/1/FU/1/2018/SME/III	Dr Kerstin Wickström and Mr Christian Gartner
15 November 2018	EMEA/H/SA/3522/2/2018/SME/III	Dr Carin Bergquist, Dr Stephan Lehr and Dr Kerstin Wickström
30 January 2019	EMEA/H/SA/3522/2/FU/1/2019/SME/III	Dr Jens Reinhardt, Dr Carin Bergquist and Dr Kerstin Wickström
12 December 2019	EMEA/H/SA/3522/2/FU/2/2019/SME/III	Dr Jens Reinhardt and Dr Kerstin Wickström
25 June 2020	EMEA/H/SA/3522/2/FU/3/2020/SME/II	Prof Andrea Laslop and Dr Kerstin Wickström
23 July 2020	EMEA/H/SA/3522/2/FU/4/2020/SME/I	Dr Jens Reinhardt and Dr Juha Kolehmainen

The Applicant received Scientific Advice on the development of Ranibizumab biosimilar to Lucentis from the CHMP on 23 March 2017 (EMEA/H/SA/3522/1/2017/SME/III). The Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

Quality:

- the proposed set of analytical studies for the comparability exercise for structure, purity, and quantity
- proposed biological assays analysing potency and binding capacity
- the approach to scale-up of manufacturing
- the proposed analytical approach to methods for the release specification of Xlucane active substance and finished product
- the proposed approach to a bridging study between primary containers

Non-clinical

- the proposed non-clinical *in vitro* potency assays
- a lack of need for *in vivo* non-clinical studies

Clinical

- the proposed approach to fulfilling the regulatory requirement of conducting a PK study

- on Phase III: the use CFT as the proposed primary endpoint for the pivotal clinical trial, the proposed secondary endpoints, the proposal for efficacy evaluation at 2 months (56 days) for the pivotal study, the proposed an equivalence margin , the proposed interim analysis procedure allowing for the sample size to be re-estimated, the proposed patient population to be included, the treatment regime, the assessment of, safety and immunogenicity is suggested to be evaluated over a 6-month period and the sample size
- the possibility for extrapolation also to the indications currently approved for the RMP Lucentis

The Applicant received Scientific Advice on the development of Ranibizumab biosimilar to Lucentis from the CHMP on 31 May 2018 (EMEA/H/SA/3522/1/FU/1/2018/SME/III). The Scientific Advice pertained to the following quality and clinical aspects:

Quality

- assays for evaluation of functional similarity

Clinical

- the proposed reference product in the Phase III clinical study
- the updated proposed choice of primary and secondary endpoints and the timing for assessments
- the updated proposed main inclusion criteria for the study population to be enrolled in the Phase III study
- a proposed non-inferiority design rather than an equivalence margin
- a proposed interim analysis procedure allowing for the sample size to be re-estimated
- the use of unblinded IMP administration in the planned Phase III comparability clinical trial
- the proposed PK sub-study in the planned Phase III clinical trial, sample size and PK sampling schedule:
- the data cut off point of the clinical data and filing strategy
- the proposed strategy for clinical evaluation of the relative immunogenicity
- the inclusion of various regions in the pivotal Phase III study

The Applicant received Scientific Advice on the development of Ranibizumab biosimilar to Lucentis from the CHMP on 15 November 2018 (EMEA/H/SA/3522/2/2018/SME/III). The Scientific Advice pertained to the following: quality and clinical aspects

Quality

- the overall plan to demonstrate biosimilarity between Xlucane and Lucentis
- the plans for demonstrating biosimilarity with the RMP across the shelf-life of the product

Clinical

- the updated proposed eligibility criteria for the study population to be enrolled in the Phase III study
- the updated secondary endpoints
- the updated proposed PK sampling schedule in the phase III clinical trial

The Applicant received Scientific Advice on the development of Ranibizumab biosimilar to Lucentis from the CHMP on 30 January 2019 (EMEA/H/SA/3522/2/FU/1/2019/SME/III). The Scientific Advice pertained to the following: quality and clinical aspects

Quality:

- adequacy of the strategy and the data accumulated for biosimilarity assessment of Xlucane to Lucentis and the use of specific tests for the evaluation of the interaction of ranibizumab with VEGF-A isoforms 110, 121, 165 and 189 to confirm functional similarity.

Clinical:

- acceptability of the equivalent margin proposed for the phase III biosimilarity trial and adequacy of safety database.

The Applicant received Scientific Advice on the development of Ranibizumab biosimilar to Lucentis from the CHMP on 12 December 2019 (EMEA/H/SA/3522/2/FU/2/2019/SME/III). The Scientific Advice pertained to the following quality and clinical aspects:

Quality

- the proposed control strategy and specification for the Xlucane presentation
- the proposed strategy for developing a sterilisation method for the Xlucane
- the proposed stability program for Xlucane DS, Xlucane DP vial presentation supporting marketing authorizationt
- the proposed acceptance criteria for comparability between the Xlucane vial presentation and other Xlucane presentation

Clinical

- the approach to assess usability to support the use of Xlucane.
- Proposal for an unblinded analysis of efficacy and safety when all patients have completed their 8-week assessments
- Interpretation of the pre-defined equivalence margin in the ongoing phase 3 clinical study

The Applicant received Scientific Advice on the development of Ranibizumab biosimilar to Lucentis from the CHMP on 25 June 2020 (EMEA/H/SA/3522/2/FU/3/2020/SME/II). The Scientific Advice pertained to the following clinical aspects:

Clinical

- The proposal to reduce the sample size of the PK sub-study in the ongoing Phase III clinical study in light of the ongoing COVID-19 pandemic to reduce the risk to patients by minimizing potential exposure to covid-19 which additional visit(s) at site(s).

The Applicant received Scientific Advice on the development of Ranibizumab biosimilar to Lucentis from the CHMP on 23 July 2020 (EMEA/H/SA/3522/2/FU/4/2020/SME/I). The Scientific Advice pertained to the following quality aspects:

Quality

- stability strategy to support the initial shelf-life determination of Xlucane
- adequacy of the program to demonstrate analytical and process comparability of Xlucane finished product vials manufactured at two sites.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jayne Crowe Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	9 September 2021
The procedure started on	30 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2021
The CHMP Co-Rapporteur's first critique was circulated to all CHMP and PRAC members on	3 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 January 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 April 2022
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	2 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	23 June 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 August 2022
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	31 August 2022
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 Ximluci on	15 September 2022

2. Scientific discussion

2.1. About the product

Ximluci has been developed as a biosimilar to the EU reference product Lucentis, solution for injection (active substance INN: ranibizumab).

2.2. Quality aspects

2.2.1. Introduction

Ranibizumab, the active substance in Ximluci, is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology.

Ximluci is presented as solution for intravitreal injection in a single-use vial. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution (strength 10 mg/mL). This provides a usable amount to deliver a single dose of 0.05 mL containing 0.5 mg ranibizumab to adult patients.

Ximluci is intended to be administered using, a sterile syringe and an injection needle (both provided separately). A filter needle for withdrawal of Ximluci from the vial is co-packaged for one of the two authorised presentations.

Ranibizumab is formulated with trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20 and water for injections.

Ximluci has been developed as a biosimilar to Lucentis (EMEA/H/C/000715).

2.2.2. Active Substance

2.2.2.1. General information

Ranibizumab is an antibody-binding fragment (Fab) of a recombinant humanised IgG1 kappa isotype monoclonal antibody. The active substance contains a light chain with 214 amino acids and a heavy chain with 231 amino acids. The two polypeptide chains are linked via an inter-chain disulphide bond. Ranibizumab does not contain the Fc region that is involved in antibody-mediated effector functions and there are no N-glycosylation sites in the molecule.

The fully assembled product has a molecular weight of approximately 48 kDa.

The active substance binds with high affinity to VEGF-A (in particular to isoforms VEGF110, VEGF121, VEGF165 and VEGF189) which are the major biologically active isoforms involved in the pathological process of age-related macular degeneration (AMD).

2.2.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The active substance is manufactured at UAB Biotechnologines, Mokslininku str, Vilnius, Lithuania. All sites involves in manufacture, QC testing and storage of the cell banks and active substance operate in accordance with EU GMP.

The manufacturing process is a standard production process for a recombinant antibody-type protein. One single active substance batch is produced from one fed-batch fermentation using a production scale bioreactor. At the end of cultivation, the temperature of the cell suspension is reduced, and the cells are disrupted using a high-pressure homogeniser. No pooling of harvests is performed. The purification process includes a series of chromatographic steps The active substance is stored in the container closure system. Single use materials (e.g. bags and filters) and their material of construction are defined. There is no reprocessing performed.

Control of materials

The raw materials for the upstream and downstream process are described, including their pharmacopoeial standards. Specifications are presented for non-compendial materials and are appropriate. The materials used to formulate the active substance are tested according to the Ph. Eur. No raw materials of human or animal origin are used in the manufacturing process. The quantitative composition of the cell culture media and solutions is provided. Membranes and resins used in the downstream process are specified in this section of the dossier and appropriate specifications are defined for these materials.

The construction of the expression plasmid, is adequately described and followed a standard approach. The expression plasmid was fully sequenced after cloning and the sequence is presented in the dossier. The source, history and generation of the cell substrate is sufficiently described.

A two-tiered cell banking system is in place. Overall, the MCB and WCB have been appropriately characterised and homogeneity of the cell banks has been established. The approach follows the recommendations of ICH Q5B and ICH Q5D.Non-compendial test methods for screening of cell banks are described and confirmation provided that they are suitably qualified. In addition, information from the end-of-production-cell-bank (EOPCB) is provided and demonstrates the genetic stability between the WCB and cells at the maximum fermentation time (limit of *in vitro* cell age). The stability of the cell banks on long-term storage is sufficiently justified and a protocol for ongoing monitoring of cell bank stability has been registered. The procedure for generation and qualification of future working cell banks is acceptable.

Control of critical steps and intermediates

Critical process parameters (CPPs) and in-process controls (IPCs) are defined with associated acceptance criteria. All other parameters are assigned set-point values throughout the manufacturing process description. The manufacturing process is adequately described and includes sufficient detail regarding process parameters and IPCs. IPC methods have been appropriately qualified. And the active substance batch size has been registered.

Process validation

In general, active substance process validation is acceptable. Consecutive active substance process validation batches were manufactured at the proposed commercial manufacturing site. Otherwise, all CPPs, PPs and IPCs passed during process validation. The results of the extended testing during upstream process validation are consistent and support a well-controlled process, e.g. consistent growth profiles, yield, culture purity and plasmid retention. Data is presented supporting sufficient clearance of process- and product-related impurities during the downstream process. Storage conditions and hold times of in-process intermediates were evaluated and support the hold times registered to 3.2.S.2.4. A protocol for confirmation of the membrane/resin lifetimes at commercial scale has been registered. The protocol is acceptable. Active substance shipping has been qualified in accordance with relevant standards.

Manufacturing process development

The main change introduced for the commercial process was the implementation of a new WCB lot which was derived from the existing MCB used to manufacture the phase 3 clinical batches.

Comparability data is presented which shows that the quality and stability of commercial active substance, phase 3 active substance and pre-phase 3 active substance are highly similar. Some minor differences were observed in quality attributes but, generally, there is an increase in purity of the active substance across development. The comparability analysis is based on a comparison of results of release tests and stability profiles. However, the extended characterisation performed as part of the analytical similarity exercise presented in 3.2.R includes both phase 3 and commercial finished product batches. Overall, the data supports that the materials are comparable as no significant differences are observed across the quality attributes evaluated and ranges observed.

Control strategy and process characterisation

The selected critical quality attributes (CQA) are appropriately justified in the dossier and are in line with the general expectations for this type of product. The impact of the process on the identified CQAs was evaluated during process characterisation. A risk assessment of all process parameters in the manufacturing process of the active substance was performed using a failure modes and effects analysis (FMEA) to identify potential CPPs (pCPPs). The scoring system for the FMEA and the cut-off threshold for the risk priority number (RPN) are discussed in the dossier and are acceptable. In general, relevant process parameters were considered during the risk evaluation and the approach is supported by the provided FMEA report.

Potential CPPs which were likely to have independent effects from other CPPs were first examined in a PP influence assessment study (PPIA). Those PPs determined to be critical in the PPIA were then studied in the CPP/CQA linkage study using a design of experiments (DOE) approach to evaluate their impact on CQAs. Overall, the general approach to process characterisation is acceptable. The acceptance ranges studied for the CPPs are consistent with the ranges registered to the control strategy in sections 3.2.S.2.2 and 3.2.S.2.4 of the dossier. The small scale models used throughout process characterisation have been justified with respect to their representativeness for the commercial scale process. The PPIA studies were provided for a number of steps and support that the PPs selected for further characterisation according to DOE are appropriate. The criteria applied during the DOE studies for designating a pCPP as a CPP follow a standard approach and are acceptable. The magnitude of effect of a pCPP on a CQA was interpreted from the effect plots of statistically generated models. A pCPP was designated as critical when the magnitude of effect was substantial within the range studied, according to the model. Responses were considered to have low magnitude of effect in cases where the variability of the responses obtained within the studied pCPP range was smaller or similar to the analytical variation expected.

The control strategy for the upstream process does not include any CPPs which has been justified. It is agreed that the feed profiles, culture durations, and control strategies applied in the upstream process result in a highly reproducible and robust fermentation process, as evidenced by observed ranges from historical batches.

In general, the control strategy for the downstream process includes appropriate CPPs during the chromatography steps. In addition, maximum resin cycles are defined as a CPPs for all chromatography steps.

The small-scale studies performed to support the biochemical stability of the process intermediate hold times were provided and are acceptable. Hold times for process intermediates have been defined as CPPs and are justified. The small-scale studies to support the resin life-times have been provided and are acceptable. An extractable study was performed for the active substance container closure is briefly described and no organic or inorganic compounds were detected above the level of toxicological

concern. A risk assessment has been presented regarding the risk of extractables and leachables from product contact materials during the active substance manufacturing process and includes results of extractable studies, where relevant. No particular risk has been identified.

Characterisation

The active substance has been appropriately characterised with respect to primary, secondary and higher order structure, binding properties and bioactivity, size distribution, charge distribution and hydrophobic/hydrophilic species. A range of physicochemical and biological tests were used. Binding characteristics and reporter gene assay activity of ranibizumab against VEGF-A isoforms 165, 110, 121 and 189 were evaluated. In addition, the bioactivity of the active substance against the predominant VEGF-A isoform 165 was characterised using a HUVEC proliferation assay. Numerous and orthogonal methods were used to evaluate primary, secondary and tertiary structure. N-linked glycans have not been specifically analysed which is acceptable because the molecule lacks the Fc region and does not contain any amino acid motifs typical for N-glycosylation. In addition, glycation of lysine residues and O-linked glycosylation was not observed.

Process-related impurities are derived from the manufacturing process and are either (i) cleared to acceptable levels according to the results of process validation or (ii) routinely controlled at IPC or release testing.

2.2.2.3. Specification

Specifications

Specifications for the active substance include control of identity, purity and impurities, potency and other general tests.

The active substance specification testing panel is generally appropriate. The specifications have been justified using an appropriate number of active substance batches. There is no particular trend observed on long-term stability and, thus, a single set of acceptance criteria based on mean -3SD for limit tests and mean ± 3SD for potency is defined in release and shelf life specifications. In general, the approach is agreed as specifications are relatively tight.

While, in principle, the specifications for control of impurities are acceptable, it was requested to revise the acceptance criteria for impurities to report to one decimal place and this has been done. It was requested to tighten the proposed specification for osmolality in line with the requested tightening of the acceptance criteria for osmolality in the finished product specifications and this has been done.

The proposed acceptance criteria for potency are consistent with the method variability observed on stability. The proposed potency specification is based on results from the analytical potency method used during development. The proposal to base the commercial potency specifications on results from an earlier version of the assay was queried. A detailed explanation of the differences between the two versions of the potency assay has been provided along with a justification as to why these differences are unlikely to impact on the potency results obtained with either method. The methods are essentially equivalent although the later version was improved to increase assay robustness. In addition, a bridging study was performed to establish equivalence of the potency methods. Results with the two methods were compared in a two-tailed paired samples t-test and the methods were found to be comparable. The data presented supports the equivalence of the methods. The proposal to retain both versions of the assay in the dossier is acceptable.

Overall, the active substance specifications are considered acceptable.

Analytical procedures

Compendial methods are used for clarity, colour, bacterial endotoxins, microbial enumeration, pH, and osmolality. Non-compendial methods are briefly described in the dossier. In general, the method descriptions are sufficiently detailed and include relevant details regarding equipment, reagents, operating conditions, sample and standard preparation, assay controls and system of suitability.

The method validation summaries provided in the dossier confirm that validation is generally in line with ICH Q2. Quality control (QC) methods will be performed at the site of method validation.

The potency assay is sufficiently described and the controls are appropriate to ensure consistent assay performance. The potency assay has been appropriately validated including an evaluation of robustness across different lots of critical reagents.

Batch analysis

Batch analysis data is presented for several active substance batches manufactured across process development and commercial process. All batches comply with the specifications in place at the time of testing.

Reference standards

A primary reference standard (PRS) has been generated from a commercial active substance lot and is qualified against the previous interim reference standard. The PRS is stored and will be retested regularly against a subset of the qualification tests addressing potency and purity. The interim reference standard has been appropriately qualified including the extended characterisation as described in section 3.2.S.3.1. Working reference standards can be generated and used for requalification of PRS and release of commercial batches.

The testing panels for qualification of new reference standards or re-qualification of existing references (both PRS and working reference standard (WRS)) have been defined and are generally acceptable. In addition, the approach for assigning potency upon the introduction or re-qualification of reference standards is appropriate.

The HCP standard used for determination of HCP in the process-specific ELISA method is described. The approach for introduction of a new HCP standard is outlined and follows the requirements of Ph. Eur. 2.6.34.

Container closure

The container closure system for storage of active substance is a pre-sterilised single-use bottle with a cap. For the resin, confirmation of compliance with the relevant foodstuff legislation has been provided. The closure resin complies with Ph. Eur. 3.1.3 and Ph. Eur. 3.1.5 which is acceptable. The suitability of the container closure is supported by the results of real-time, accelerated and stressed stability studies (section 3.2.S.7.3) and the extractables study results as discussed in section 3.2.S.2.6. The specifications for the container closure are acceptable.

2.2.2.4. Stability

The proposed shelf-life of the active substance is acceptable.

There is no trend observed for any active substance quality attribute under any storage condition tested.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is presented in a single-use type I glass vial with a bromobutyl rubber stopper. In the initial submission a pre-filled syringe (PFS) was proposed as an additional presentation. The PFS presentation has subsequently been withdrawn.

The finished product is a clear to slightly opalescent, colourless to slightly brownish, sterile and preservative free aqueous solution.

Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution.

Ximluci is intended for intravitreal administration using:

- A sterile, blunt 5 µm filter needle (18G x 1½″ , 1.2 mm x 40 mm) (co-packed);

- A 1 mL sterile syringe (including a 0.05 mL mark) (provided separately);

- An injection needle (30G x ½″ , 0.3 mm x 13 mm) (provided separately).

The list of excipients is presented in section 6.1 of the SmPC. No novel excipient is used and they are all of Ph. Eur. grade.

Pharmaceutical development

The Ximluci finished product formulation was developed to mimic the reference medicinal product (RMP) Lucentis. The excipients and formulation are identical for the active substance and the finished product. The physico-chemical properties are demonstrated to be clinically relevant for the patient in the RMP. There are no materials of animal or human origin.

The process flow for the finished product manufacturing is clearly outlined and there is a good understanding of the risks and CQAs identified at each stage of the process. A summary and justification for the proposed CPPs based on the identified CQAs is provided and considered acceptable. Active substance thawing studies at both sites determined the thaw time and holding temperature. Mixing speeds and times were developed Details on the investigation of the filter compatibility, and the filter suppliers is provided. Extractable studies were performed on the systems for sterile filtration and levels extracted were considered safe in accordance with ICH Q3C (R8), this is acceptable.

Engineering batches clinical batches, and additional GMP batches, of Ximluci finished product were manufactured. The process was subsequently transferred to the commercial site where engineering and process validation batches were manufactured. Process changes in the transfer are site specific and clearly described. Process characterisation studies were carried out on batches from the former site, and process validation batches from the commercial site. Comparability was based on finished product release data, extended characterisation and stability study data. Extended characterisation included size distribution, secondary structure, tertiary structure, and thermal stability. The characterisation parameters selected for the comparability study are considered acceptable and the data provided indicates good comparability between finished product manufactured at both sites.

The container and closure for the single use vial presentation was selected to mimic the RMP and is composed of a type I clear borosilicate glass 2R vial, a bromobutyl rubber stopper and an aluminium seal with flip-off cap. The vial and stopper comply with the relevant Ph. Eur. monographs. The suitability of the primary packaging components has been confirmed by compatibility studies on the vial and the stopper. No volatile, semi-volatile or non-volatile organic compounds were detected above the analytical evaluation threshold (AET) level in the extractables study, a leachables study for the

primary container is not proposed and this is considered acceptable. The finished product comes as a vial-only pack or packaged with a CE marked sterile 5 µm filter needle required to withdraw the product from the vial. Compatibility studies are provided and considered acceptable.

2.2.3.2. Manufacture of the product and process controls

Manufacture

Sites responsible for the manufacture, control and storage of the finished product operate in accordance with EU GMP. STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany is responsible for final EU batch release.

The manufacturing process for the vial presentation is described and a flow chart detailing CPPs, and IPCs at each unit operation is provided.

The manufacturing process is standard and includes thawing of active substance, compounding with formulation buffer followed by sterile filtration through two sterile filters in series and filling into pre-sterilised vials. There is 100% visual inspection of all filled vials The active substance thaw and hold time is considered acceptable. The time out of refrigerator during visual inspection and secondary packaging is adequately justified. No reprocessing is proposed.

Process controls

The manufacturing process is controlled by CPPs at the buffer preparation, sterile filtration, filling, inspection and labelling stages. The process is controlled by IPCs at the buffer preparation, sterile filtration and filling stages. The CPPs and IPCs were developed based on a quality target product profile (QTPP). A risk management overview and the process impact at each stage in the manufacturing is described and considered acceptable. The approach to be followed when CPPs or IPCs fail to meet acceptance criteria is acceptable.

Process validation

Data are provided for consecutive, commercial scale batches manufactured and filled into vials. Details are provided for the active substance batches used to manufacture the finished product. Details of the mixing are provided and considered acceptable.

The transport validation/verification system is considered acceptable. A summary of the outcome of the proposed lab-based transport validation study proposed to be provided post authorisation and this can be addressed as a recommendation.

2.2.3.3. Product specification

Specifications

Specifications for the finished product include control of identity, purity and impurities, potency and other general tests.

Specifications proposed for the finished product release are identical to the shelf life specifications proposed for the stability studies in P.8.1. General tests are included for appearance, visible particles, sub-visible particles, pH, osmolality, and container closure integrity. Suitable justification is provided for the finished product release specifications. Purity and impurity are determined. Contaminants are controlled by endotoxin testing and sterility. Potency and protein concentrations are determined. Overall, the testing proposed is generally appropriate and in accordance with the principles of ICH Q6B and the Ph. Eur. monograph 2031 ‘monoclonal antibodies for human use’.

The specifications for the finished product are considered acceptable.

Analytical procedures

The analytical procedures used for release and shelf life testing of the finished product are the same as for the active substance, and described in the respective active substance section. Additional methods used for DP release testing are the container closure integrity and sub-visible particles testing. Method validation is provided for the container/closure integrity testing and considered acceptable. Overall, the information provided is considered acceptable.

Batch analysis

Batch analysis data is provided for finished product batches manufactured. All batch data presented met the proposed specifications in place at the time of lot disposition. The batch analysis data presented for the process validation batches comply with the limits in the proposed commercial finished product specification. Results from these finished product lots show consistency and uniformity of the drug product and indicate that the process is under control.

Container closure

The container closure consists of a type I clear borosilicate glass 2R vial that is sealed with a rubber stopper and capped with an aluminium cap. Adequate descriptions are provided for the components. Schematics, specifications and example CoA are provided. The components are manufactured in accordance with the appropriate Ph. Eur. monographs and are acceptable. The extractables study is provided and a leachables study is not proposed, and this is considered acceptable. A filter needle can be supplied with the vial and details are registered in P.7. A CE certificate for the filter needle has been provided.

Characterisation of impurities

Analysis for elemental impurities showed no inorganic elements of concern above the respective 30 % permitted daily exposure levels according to ICH Q3D. This is acceptable.

A detailed risk assessment regarding the potential presence of nitrosamines in Ximluci was provided. Evaluation was carried out at each stage of the upstream and downstream active substance manufacturing and the finished product manufacturing process. Based on the outcome of the evaluation, the Applicant concludes that the risk for presence of nitrosamines impurities in the vial presentation is negligible and no action is required. This conclusion is considered adequately supported based on the information provided and is in accordance with the requirements of EMA/369136/2020 and EMA/409815/2020 Rev. 7.

2.2.3.4. Stability of the product

A total of three batches of long term data is provided in support of a proposed 36 month shelf life at 5±3°C for the Ximluci finished product vial presentation. In addition, supporting data is provided for engineering batches. The batches on the stability study were manufactured at a representative batch size.

Stability studies are carried out in accordance with current ICH guidelines. Batches were manufactured to commercial scale. The container closure used for the stability studies is identical to that used for the commercial product. Details on changes to the analytical methods used in the stability studies over the course of Ximluci development are outlined.

Detailed summaries of the results and trending observed for each parameter for each batch on long term stability is provided in the dossier. Results for all stability indicating parameters for engineering

batches and process validation batches are within the acceptance criteria tested under long term storage conditions. Trending data shows the product is stable with over time. The proposed shelf life is further supported with data from accelerated studies and stressed studies.

The shelf life of 36 months (2 °C – 8 °C) is considered to be adequately supported. Stability data are provided for batches for 36 months, and for batches manufactured up to 12 months. Comparability between both manufacturing sites has been demonstrated, therefore the shelf life can be leveraged from the batches. Nonetheless, it is expected that ongoing studies from the site are completed to confirm the shelf life.

In-use stability data is provided for two clinical batches. Finished product in its primary packaging is stable for 48 hours at room temperature (25°C).

2.2.3.5. Biosimilarity

A comprehensive analytical similarity study was performed by the Applicant for the purpose of demonstration of biosimilarity at the quality level between the proposed biosimilar product Ximluci, EU sourced Lucentis reference product and US sourced Lucentis. The biosimilarity exercise included a side-by-side comparative analytical assessment (batches of EU Lucentis, batches of US Lucentis and batches of Ximluci –) and stability studies to compare degradation profiles.

The Applicant's approach for demonstrating biosimilarity is aligned with the relevant CHMP guidelines and thus considered acceptable. The selection of batches and assignment of CQAs for the comparative assessment is presented in a clear logical manner and is considered acceptable.

The methods used for biosimilarity assessment are predominantly statistical, and include the following: fixed limits (mass spectrometry analysis, amino acid analysis, binding of other members of the VEGF family by SPR), quality range approach (QAs with quantitative results), min-max of reference product and equivalence testing (as supportive information for QAs with high/very high criticality such as binding by surface plasmon resonance (SPR) and bioactivity by gene reporter assay). Visual assessment was used for chromatographic analysis.

The vast majority of attributes (strength, bioactivity, binding, and product related species) assessed were compared using the defined quality range and comparison of the results of the Ximluci finished product batches against the min-max ranges of EU Lucentis and US Lucentis batches. In general, the quality attributes analysed were shown to be highly similar between XSB-001 and both EU and US Lucentis. A large panel of methods has been used to characterise and compare the most relevant physicochemical and biological quality attributes of the ranibizumab molecule.

The results of the comparative analytical assessment (Table 1) demonstrated that the primary and higher order structure, functionally binding and bioactivity to four isoforms of VEGF A of Ximluci finished product is highly comparable to EU Lucentis and US Lucentis. For purity and related species, some minor differences were observed in Ximluci batches, predominantly in engineering batches manufactured using a process which has subsequently been modified slightly to improve purity and are not considered to have any meaningful impact. Any differences identified were considered minor and were in general sufficiently justified, hence do not impact on the biosimilarity claim.

The stability testing included accelerated (+25°C ±2°C / 60 % RH ± 5% RH), stressed (+40°C ±2°C / 75% RH ± 5% RH) and forced degradation studies at low and high pH, oxidative, agitation, freeze-thaw cycling, normal and UV-light stress conditions. All these studies were conducted with three batches each of Ximluci, EU Lucentis and US Lucentis. In general the results show that while some minor differences were detected in the rates of degradation/levels of degradants, particularly for the

forced degradation studies, overall similar degradation profiles were observed, further supporting similarity across Ximluci, EU and US Lucentis.

Summaries of the methods used in the comparative analytical assessment studies are provided in the dossier. Additionally, following a query raised, suitable qualification data was provided for all methods.

In summary, the data presented support similarity between Ximluci and both EU and US Lucentis. Biosimilarity is considered demonstrated.

Table 1: Summary of analytical biosimilarity exercise

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
Attributes related to primary structure, disulfide linkages and identity	Very High	Intact protein mass (Da)	SEC-HPLC-MS	Fixed: all values within theoretical mass ±2 Da	All XSB-001 DP, EU Lucentis, and US Lucentis batches passed the acceptance criteria of the assessment for protein mass.
		Light chain mass (Da)		Fixed: all values within theoretical mass ±1 Da	
		Heavy chain mass (Da)		Fixed: all values within theoretical mass ±1 Da	
		Amino acid sequence coverage	Reducing peptide map, LC-MS	Fixed: Light chain: 100% coverage Fixed: Heavy chain: 100% coverage	Data demonstrated identical sequences for the heavy chain as well as for the light chain of XSB-001 DP, EU-Lucentis, and US Lucentis.
		Reducing peptide map profile		Visual: Similar, no major peaks present/absent	
		Disulfide linkages	Non-reducing peptide map, LC-UV	Fixed: 5 disulfide containing peptides are observed	All tested batches displayed the five peaks corresponding to the expected peptides linked by disulfide linkages
		Non-reducing peptide map profile		Visual: Similar, no major peaks present/absent	
		N-terminal sequence	Reducing peptide map, LC-MS	Fixed: ≥10 terminal amino acids confirmed	Data demonstrates identical N-and C-terminal sequences for the heavy chain as well as for the light chain of XSB-001 DP, EU Lucentis and US Lucentis.
		C-terminal sequence		Fixed: ≥10 terminal amino acids confirmed	

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
		Isoelectric point	cIEF	QR: all values within mean ±2 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable to US Lucentis.
	High	Non-canonical Amino Acids	Hydrolysis, derivatization and HPLC	Not detected	Neither Nle nor Nva was detected on analysis in any of the batches of XSB-001 DP, US Lucentis, and US Lucentis subjected to amino acid analysis and thus the acceptance criteria 'not detected' was passed.
	Low	Amino Acid Composition	Hydrolysis, derivatization and HPLC	±2 amino acids from theoretical amino acid ratio	The observed mole ratio of amino acids is comparable between XSB-001 DP, EU Lucentis, and US Lucentis.
		N-terminal sequence	Edman sequencing	Fixed: 10 terminal amino acids confirmed	The 10 terminal amino acids were confirmed for all XSB-001 DP, EU Lucentis and US Lucentis batches
Higher order structure	High	Thermal stability (°C)	DSC	QR: all values within mean ±2 SD Evaluate against MIN-MAX	The thermal stability of XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Thermal stability profile		WSD below detection threshold for differences	

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
		Near UV circular dichroism profile	CD spectroscopy	WSD below detection threshold for differences	The tertiary structures of XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Far UV circular dichroism profile		WSD below detection threshold for differences	The secondary structures of XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Fourier-transform infra-red profile	FTIR spectroscopy	WSD below detection threshold for differences	The secondary structure of XSB-001 DP, EU Lucentis and US Lucentis are comparable.
Strength	High	Protein concentration (mg/ml)	Spectrophotometric	QR: all values within mean ±2 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable to US Lucentis.
Bioactivity and binding	Very High	Bioactivity, VEGF-A 165 (%)	Reporter gene assay	QR: all values within mean ±2 SD Evaluate against MIN-MAX	All XSB-001 DP batches were within the quality range defined by pooled EU Lucentis data. All except one XSB-001 DP batch were within the quality range defined by pooled US Lucentis data. The slight excursion for the XSB-001 DP batch outside US Lucentis quality ranges was not considered significant. The overall

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
					conclusions are that XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable to US Lucentis.
	High	Binding, VEGF-A 165 (%)	SPR	QR: all values within mean ±2 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable to US Lucentis.
	Moderate	Bioactivity, VEGF-A 110 (%)	Reporter gene assay	QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable to US Lucentis.
		Bioactivity, VEGF-A 121 (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	
		Bioactivity, VEGF-A 189 (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	
		Bioactivity, VEGF-A 165 (%)	HUVEC proliferation assay	QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable to US Lucentis.
		Binding, VEGF-A 110 (%)	SPR	QR: all values within mean ±3 SD	XSB-001 DP is comparable with both EU Lucentis

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
				Evaluate against MIN-MAX	and US Lucentis and that EU Lucentis is comparable to US Lucentis.
		Binding, VEGF-A 121 (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	
		Binding, VEGF-A 189 (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	
Binding to members of VEGF family	Very low	Binding to VEGF-B	SPR	Fixed No significant binding is observed	The Fab in XSB-001 DP and Lucentis do not bind to other members of the VEGF family.
		Binding to VEGF-C		Fixed No significant binding is observed	
		Binding to VEGF-D		Fixed No significant binding is observed	
		Binding to PlGF		Fixed No significant binding is observed	
Aggregates	High	Main Peak (%)	SE-HPLC	QR: all values within mean ±2 SD Evaluate against MIN-MAX	Despite the excursion of a single XSB-001 DP batch towards the EU Lucentis and US Lucentis quality ranges, XSB-001 DP is comparable with both EU Lucentis and US Lucentis. It is also concluded that EU Lucentis, despite the

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
					excursion of one batch, is comparable with US Lucentis.
		High molecular weight species (%)		QR: all values within mean ±2 SD Evaluate against MIN-MAX	Despite the excursion of a single result for XSB-001 DP, XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis, despite the excursion of one batch, is comparable with US Lucentis.
		Size exclusion chromatographic profile		Visual evaluation to support conclusions from numerical SEC-HPLC data	The SE-HPLC chromatographic profiles indicates a high degree of similarity between XSB-001 DP, EU Lucentis, and US Lucentis.
		Analytical ultra-centrifugation profile	AUC	Visual: Similar profile	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable with US Lucentis.
		High molecular weight species (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable with US Lucentis.
Charge variants	High	Main Peak (%)	SCX-HPLC	QR: all values within mean ±2 SD Evaluate	XSB-001 DP originating from DS manufactured by using more

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
				against MIN-MAX	mature versions of the purification process is comparable with both EU Lucentis and US Lucentis.
		Acidic species (%)		QR: all values within mean ±2 SD Evaluate against MIN-MAX	XSB-001 DP is comparable to both EU Lucentis and US Lucentis and that EU Lucentis is comparable to US Lucentis.
		Basic species (%)		QR: all values within mean ±2 SD Evaluate against MIN-MAX	XSB-001 DP originating from DS manufactured by using more mature versions of the purification process is comparable with both EU Lucentis and US Lucentis.
		Cation exchange chromatographic profile		Visual evaluation to support conclusions from numerical SCX-HPLC data	The chromatographic profiles indicate a high degree of similarity between XSB-001 DP, EU Lucentis and US Lucentis.
	Moderate	Main Peak (%)	cIEF	QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable with US Lucentis.
		Acidic variants (%)		QR: all values within mean ±3 SD Evaluate	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
				against MIN-MAX	comparable with US Lucentis.
		Basic variants (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and that EU Lucentis is comparable with US Lucentis.
Hydrophilic and Hydrophobic species	Moderate	Main Peak (%)	RP-HPLC	QR: all values within mean ±3 SD Evaluate against MIN-MAX	Despite a few batches of XSB-001 DP being slightly outside the comparability ranges, XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Hydrophilic species (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	Despite excursions observed for three batches of XSB-001 DP, XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Hydrophobic species (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	Despite excursions observed for two XSB-001 DP batches, XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Reversed phase chromatographic profile		Visual evaluation to support conclusions from numerical RP-HPLC data	There is a high similarity in chromatographic profiles and no unique peaks are observed in the studied batches of XSB-001 DP, EU

Characteristics	Criticality	Associated Quality Attributes (Unit)	Method	Assessment Method and Comparative Assessment Range	Conclusion
					Lucentis, and US Lucentis.
Size variants	Low	Purity (%)	Non-reducing CGE	QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Fragments (%)		QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP, EU Lucentis and US Lucentis are comparable.
		Purity (%)	Reducing CGE	QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP, EU Lucentis and US Lucentis are comparable.
Free thiols	Low	Free thiols (mol/mol protein)	Fluorometric assay	QR: all values within mean ±3 SD Evaluate against MIN-MAX	XSB-001 DP is comparable with both EU Lucentis and US Lucentis and EU Lucentis is comparable with US Lucentis.

2.2.3.6. Post-approval change management protocol(s)

A post-approval change management protocol (PACMP) is proposed for the scale-up of active substance manufacture by a factor of 10.

Three consecutive validation batches are planned to support the scale-up. All of the final CPPs/PPs will be verified and reported for the process validation batches. In addition, the FMEA performed to verify that no change to manufacturing process controls is required was provided and supports the proposed approach. The proposal to verify the proposed in-process hold times and temperatures as part of the process validation is acceptable. Active substance batches will be included in a long-term and accelerated conditions stability program. An updated risk assessment for extractables and leachables will be performed which is agreed.

Comparability of the current and proposed process will be evaluated by in-process data and release testing of active substance from the validation batches. The testing panel for comparability includes release tests and additional extended characterisation tests. Results from historical process batches will be included in the comparability exercise and used to generate comparability acceptance criteria. The testing panel and acceptance criteria for the comparability exercise have been registered to the

PACMP and are acceptable. Historical process batches will be statistically evaluated for quantitative quality attributes and the acceptance criteria will be based on mean ±3SD for all CQAs except when this is not feasible for the method. In the latter case, the Min-Max range will be used.

The PACMP proposed for the scale-up of the active substance manufacturing process is considered acceptable.

Following the withdrawal of the PFS presentation during the procedure, the Applicant proposed a PACMP for the future registration of the PFS presentation. However, numerous deficiencies were noted in the PACMP. While some aspects could be addressed by significant revision of the PACMP, there were numerous issues that did not appear to be resolvable. As a consequence, the Applicant decided to remove the PACMP for the PFS from the dossier.

2.2.3.7. Adventitious agents

The active substance is produced by bacterial fermentation, which does not support the growth of viruses.

No materials or excipients of biological origin are used in the active substance and finished product manufacturing processes.

The cell banks have been screened for microbiological purity and absence of bacteriophage has been confirmed.

TSE certificates have been provided for the active substance, finished product and for the components of the active substance/finished product formulation and are acceptable.

The control strategy for microbial purity and endotoxins is described and is acceptable. Animal-derived materials were used in the product of the butyl rubber stopper. Statements are provided confirming that these materials are in compliance with EMEA/410/01 Rev. 3.

It is agreed that the risk of viral contamination is negligible. The risk of TSE transmission is also negligible.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance manufacturing process is standard, adequately described and appropriately validated. The active substance has been appropriately characterised with respect to primary, secondary and higher order structure, binding properties and bioactivity, size distribution, charge distribution and hydrophobic/hydrophilic species. The active substance specifications and proposed analytical methods are acceptable. The proposed active substance shelf-life is acceptable.

A PACMP is proposed for the scale-up of active substance manufacture by a factor of 10. The PACMP is acceptable.

The active substance is produced by bacterial fermentation. No materials or excipients of biological origin are used in the active substance and finished product manufacturing processes. Statements are provided confirming that animal-derived materials used in the manufacture of finished product primary packaging are in compliance with EMEA/410/01 Rev. 3. It is agreed that the risk of viral contamination or TSE transmission is negligible.

The Ximluci finished product is presented as a single-use vial. In the initial submission a PFS was proposed as an additional presentation. The PFS presentation was subsequently withdrawn. The Applicant proposed a PACMP to introduce the PFS presentation and this has also been withdrawn.

Information on the finished product formulation is provided and acceptable. Overall, the pharmaceutical development of the vial presentation is acceptable. Engineering batches, clinical batches, and additional GMP batches of Ximluci finished product were manufactured. The process was subsequently transferred to the commercial site where process validation was performed. Process changes in the transfer are site specific and clearly described. Comparability studies are well described and indicate good comparability of the finished product from both sites. The container and closure was selected to mimic the RMP single use vial presentation and is composed of a type I clear borosilicate glass 2R vial, a rubber stopper and an aluminium seal with flip-off cap. The vial and stopper comply with the relevant Ph. Eur. monographs.

The finished product manufacturing process is described and a flow chart detailing CPPs, and IPCs at each unit operation is provided. The manufacturing process is standard and includes thawing of active substance, compounding with formulation buffer followed by sterile filtration through two sterile filters in series and filling into pre-sterilised vials. The manufacturing process is adequately controlled and the approach to be followed when CPPs or IPCs fail to meet acceptance criteria is described. Data are provided for three consecutive, commercial scale batches manufactured at the site and filled into vials.

Specifications are proposed for the finished product release and are identical to the shelf life specifications proposed for the stability studies in P.8.1. The specifications are acceptable and in accordance with the Ph. Eur. 2031. A risk evaluation concerning the presence of nitrosamine impurities in Ximluci is provided and considered acceptable.

Batch analysis data is provided for finished product batches. All batch data presented met the proposed specifications in place at the time of lot disposition.

The container closure consists of a type I clear borosilicate glass 2R vial that is sealed with a bromobutyl rubber stopper and capped with an aluminium cap. Adequate descriptions are provided for the components. Schematics, specifications and example certificates of analysis are provided. The components are manufactured in accordance with the appropriate Ph. Eur. monographs and are acceptable.

The finished product shelf life of 36 months is considered to be adequately supported. The finished product in its primary packaging is stable for 48 hours at ambient conditions.

The Applicant’s approach for demonstrating biosimilarity is aligned with the relevant CHMP guidelines and thus considered acceptable. The selection of batches and assignment of criticality of quality attributes for the comparative assessment is presented in a clear logical manner. In general, the quality attributes analysed were shown to be highly similar between Ximluci and both EU and US Lucentis.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Ximluci is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Ximluci is considered 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 points for investigation.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Ximluci (XSB-001/ranibizumab) is a recombinantly produced Fab fragment of the humanized monoclonal antibody (rhuMAb) that binds and neutralizes VEGF-A. It has been developed as a biosimilar to the reference product Lucentis (ranibizumab; Novartis Eurpharm Limited) authorised in the EU.

In order to demonstrate similarity to the reference product, the applicant has performed several *in vitro* studies. Binding of Ximluci, EU Lucentis and US Lucentis to VEGF-A was assessed by surface plasmon resonance measurements. Comparability assessment of bioactivity was by means of a reporter gene assay involving KDR/NFAT-RE HEK293 cells. The suitability of the reporter gene assay was verified by using a HUVEC proliferation assay. Four different isoforms of VEGF-A were included in the studies and most weight was given to the results for the predominant isoform 165. In general, binding and bioactivity of Ximluci were within the defined comparative assessment ranges for the reference products, suggesting similarity.

The assessment of biosimilarity of Ximluci and Lucentis will be primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted. The submitted nonclinical pharmacology studies do not suggest a significant difference between Ximluci and the reference products tested.

Ximluci and Lucentis did not bind to other members of the VEGF family (VEGF-B, VEF-C, VEGF-D, and PIGF-1).

No safety pharmacology or PD drug-drug interaction studies have been performed. This is considered acceptable for a biosimilar application.

2.3.2. Pharmacokinetics

A GLP-compliant study (study 5701026) was conducted in male NZW rabbits to compare the pharmacokinetics of Ximluci to the reference product, Lucentis. Each test item was administered as a single bilateral IVT injection to eight male NZW rabbits at a dose of 0.5 mg/eye (50 µL/eye). For pharmacokinetic analysis, serum concentrations of Lucentis and Ximluci were determined. In addition, concentrations of the drugs were measured in ocular tissues.

Characterisation of the pharmacokinetics of Ximluci and Lucentis in NZW rabbit serum, vitreous humor and sensory retina showed that concentration profiles and PK parameters were similar between Ximluci and Lucentis. The highest Ximluci/ranibizumab exposure in both groups was found locally in the eye, with comparable systemic exposures in serum. The results support the biosimilarity of Ximluci to RMP Lucentis.

No metabolism, excretion or PK interaction studies were conducted as part of this application, in line with biosimilar development guidelines (EMA/CHMP/BMWP/403543/2010).

2.3.3. Toxicology

A GLP-compliant, comparative single dose study in male NZW rabbits (Study 5701026) was performed to compare the toxicity profiles of Ximluci and Lucentis. A full toxicological assessment was not performed, but clinical signs, body weights, and appetence were monitored and histopathology of ocular tissues, ophthalmologic examinations and electroretinograms (ERGs) were performed.

Overall, the study indicated that a single bilateral intravitreal injection of Ximluci or Lucentis was well tolerated with no abnormal clinical signs or changes in body weights, appetite, or ERG parameters. Ophthalmic observations in the group that received Lucentis included transient uveitis or interior chamber inflammation in two animals. Minor conjunctival hyperemia was noted in animals from both Ximluci and Lucentis groups on Day 2, and was attributed to the IVT procedure. No ophthalmic observations related to Ximluci were observed. Mononuclear cell infiltration to ocular tissues occurred in both test item and reference groups, with an increased incidence and severity in the eyes administered Lucentis compared to the eyes administered Ximluci. The results support the similarity of Ximluci to Lucentis. In addition, Ximluci is formulated using the same excipients as Lucentis and therefore, no additional unanticipated toxicity is expected.

The comparative quality and nonclinical *in vitro* assessment of Ximluci did not identify any significant concerns in relation to biosimilarity to the reference product and, as the *in vitro* assays may be more specific and sensitive than studies in animals, the results of this *in vivo* study were not considered necessary from a nonclinical perspective to support the MAA.

No genotoxicity, reproductive toxicology or carcinogenicity studies have been performed and, as outlined in the relevant guidance, these are not necessary for biosimilars (EMA/CHMP/BMWP/403543/2010).

2.3.4. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for not submitting ERA studies on the basis that ranibizumab (XSB-001) is a protein, which is in line with the EMA guidance (EMEA/CHMP/SWP/4447/00 corr 2).

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Ximluci is not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

The non-clinical package to support the MAA includes *in vitro* assays (receptor-binding studies and cell-based bioassays and) as well as an *in vivo* comparative, single-dose study evaluating PK and toxicity profiles of Ximluci and Lucentis in NZW rabbits. Data are considered in the context of the demonstration of biosimilarity to Lucentis, and of the applicable guidelines.

Pharmacology

The nonclinical pharmacology assessment comprised of (1) a quantitative comparison of Ximluci DP and Lucentis *in vitro* binding to different VEGF-A isoforms using an SPR/Biacore assay, (2) functional comparisons between Ximluci and Lucentis capacities to inhibit VEGF-signalling using the VEGFR2 HEK293-cell reporter gene assay (HEK293/RGA) and (3) measurement of the proliferative response of Human Umbilical Vascular Endothelial Cells (HUVEC) to VEGF-A by Ximluci and Lucentis. The results of the *in vitro* studies are sufficient from a non-clinical point of view to demonstrate similarity between Ximluci and the reference product, Lucentis. The absence of secondary PD, safety pharmacology or PD drug interactions is in line with relevant guidance.

Pharmacokinetics

PK profiles of Ximluci and Lucentis were assessed following a single bilateral intravitreal injection in NZW rabbits. Characterisation of the pharmacokinetics in serum, vitreous humour and sensory retina showed that concentration profiles and PK parameters were similar between Ximluci and Lucentis. This

study was not deemed necessary to support the MAA. The absence of metabolism, excretion or PK interaction studies is acceptable in accordance with relevant guidance.

Toxicology

A GLP-compliant, single-dose non-clinical *in vivo* toxicology study of limited scope was completed to support regulatory approval outside the EU. The study indicated that Ximluci is similar to the reference product Lucentis with respect to tolerability following a single bilateral IVT injection of NZW rabbits. In accordance with relevant guidance and CHMP scientific advice provided to the applicant, the results of this study were not considered necessary from a nonclinical perspective to support the MAA. The proposed texts for sections 4.6 and 5.3 are in line with that of the reference product.

2.3.6. Conclusion on the non-clinical aspects

The non-clinical data support biosimilarity of Ximluci vs the reference product Lucentis and the MAA is considered approvable from a non-clinical perspective.

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: Listing of Clinical Studies

Type of study	Study identifier	Location of study report	Objective of study	Study design and type of control	Test product(s); Dosage regimen and route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment
PK Safety Efficacy Immuno-genicity	XRB1001 (Xplore)	5.3.5.1	Primary Objective: Demonstrate that the biosimilar candidate XSB-001 DP is equivalent to Lucentis in subjects with wAMD as assessed by the change in BCVA from Baseline to Week 8. Secondary Objectives: • Evaluate the efficacy of XSB-001 DP vs Lucentis in subjects with wAMD based on CFT measured by SD-OCT, area of choroidal neovascularization, and presence of leakage assessed by fundus FA • Evaluate the safety of XSB-001 DP vs Lucentis • Evaluate the systemic exposure of XSB-001 DP vs Lucentis in subjects participating in PK evaluation • Evaluate immunogenicity (i.e., ADA and NAb) of XSB-001 vs Lucentis	Phase 3 Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy, Safety, Immunogenicity and Pharmacokinetics of XSB-001 DP versus Lucentis in Patients with wAMD	XSB-001 DP: 0.5 mg in 0.05 mL solution every 4 weeks/monthly EU-Lucentis: 0.5 mg in 0.05 mL solution every 4 weeks/monthly Intravitreal (IVT) injection	583 (including 70 for PK assessment)	Patients with wAMD, ≥50 years of age	52 weeks or 13 doses

ADA = anti-drug antibodies; CFT = central foveal thickness; EU = European Union; FA = fluorescein angiography; Nab = Neutralizing antibodies; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; US = United States; wAMD = Neovascular (wet) Age-Related macular Degeneration

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Bioanalytical methods

Bioanalytical report PK

The Applicant employed an ECL immunoassay for the detection and quantitation of Xlucane (ranibizumab) in Human plasma. While 209 samples were collected, due to errors which have been sufficiently documented results from only 205 samples are reported. A short description of the run procedure and the run acceptance criteria has been provided, this is considered appropriate. No deviations for the standard operating procedure (SOP) were reported. Overall, the data provided is in line with the EU guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1).

Analytical Method Validation PK

The Applicant has provided a validation report outlining the processes employed for the validation of the assay for the quantitation of Xlucane and of the originator Lucentis in human plasma. The assay used for the quantitation of Ranibizumab was electrochemiluminescence (ECL) immunoassay. The steps of the ECL immunoassay have been well described and the method is considered adequate for the quantification of Ranibizumab. The run acceptance criteria have been defined for precision and accuracy, specificity, selectivity, dilution linearity and stability and validation data have been provided for each.

Bioanalytical Report ADA and NAb

The Applicant has provided data for the detection of anti-drug antibodies (ADA) and neutralising antibodies (NAb) to ranibizumab in human serum. For the ADA assay, a bridging format was used to

determine if anti-ranibizumab antibodies were present in the sample, if samples were found positive in the screening step then a confirmatory assay re-assessed these positive samples through the addition of unlabelled ranibizumab to determine if the assay signal was inhibited. If the samples were deemed positive, a titration assay semi-quantified the antibody response by determining a titre for signal inhibition. All samples confirmed positive in the ADA confirmatory assay were analysed for the presence of NAbs. It is noted that there were a small number of SOP deviations, however, they were all justified by the Applicant and deemed acceptable.

Analytical Method Validation ADA

In the validation report for the ADA assay, the positive control is an affinity purified rabbit polyclonal IgG antibody against Ximluci spiked into the negative control pool; the negative control is human serum from healthy non-elderly individuals. A screening cut point has been established using a floating cut point approach. The screening cut point data was generated using 50 lots of healthy human serum. The confirmatory cut point has been established using 50 samples with a 1% false positive rate. A confirmatory cut point of 16.255% was determined where above this value the samples are deemed positive for ADAs and below they are considered negative for ADAs.

Analytical Method Validation Nab

The Applicant is using an electrochemiluminescence method whereby samples and controls are first incubated with biotinylated Ximluci. The anti-ranibizumab neutralizing antibodies bound to biotinylated Ximluci are captured on a streptavidin-coated ELISA plate. The antibodies are eluted and incubated with ruthenylated Ximluci in a streptavidin plated coated with biotinylated VEGF. The signal generated from reading this plate has an inverse relationship with the level of anti-ranibizumab neutralizing antibodies. A cut point factor for the neutralising assay was determined using 50 lots of human serum.

Biosimilarity

Study XBR1001 was a Phase III double-blind parallel, group, multicentre study which compared the efficacy and safety of Ximluci (Xlucane) versus EU-licensed Lucentis® in patients with wAMD (aged ≥50 years). Subjects received either Ximluci (0.05 mL of 10 mg/mL ranibizumab) or Lucentis (0.05 mL of 10 mg/mL ranibizumab) in the study eye once every 4 weeks/monthly. The assigned study drug was administered by IVT injection.

While the main efficacy and safety results are discussed in sections below, two of the secondary objectives of this study were as follows:

- To evaluate the systemic exposure of Ximluci vs Lucentis in subjects participating in pharmacokinetic evaluation;
- To evaluate immunogenicity (i.e. anti-ranibizumab antibodies (ADAs) and neutralizing ADAs) of Ximluci vs Lucentis.

. The results for the PK and immunogenicity objectives are outlined below.

Pharmacokinetics

40 subjects in the Ximluci group and 30 subjects in the Lucentis group were included in the PK sub-study. The demographics and baseline disease characteristics for the PKS were similar between the Ximluci group and the Lucentis group.

Descriptive statistics for PK plasma ranibizumab concentrations for the PKS are presented in Table 3. The plasma ranibizumab concentrations were similar between the Ximluci and Lucentis groups at Day 1 and Week 20.

Table 3: Pharmacokinetic Plasma Ranibizumab Concentrations – Descriptive Statistics (Pharmacokinetic Set)

Ranibizumab Concentrations (pg/mL) Time point Statistic	Xlucane N=40	Lucentis N=30
Baseline		
n	38	29
BLQ	38 (100)	28 (96.6)
Mean (SD)	0 (0)	54.8 (295.3)
CV (%)	NA	538.5
Median	0	0
Min, Max	0, 0	0, 1590
Day 1		
n	40	29
BLQ	3 (7.5)	2 (6.9)
Mean (SD)	2230 (1429)	2190 (1336)
CV (%)	64.0	61.2
Median	2180	2370
Min, Max	0, 8060	0, 4780
Week 20		
n	32	24
BLQ	1 (3.1)	0
Mean (SD)	2450 (1384)	2150 (1233)
CV (%)	56.5	57.4
Median	2370	1740
Min, Max	0, 6350	397, 6170

Abbreviations: BLQ, below the lower limit of quantification; CV, coefficient of variation; Max, maximum; Min, minimum; NA, not applicable; PKS, pharmacokinetic set; SD, standard deviation.

Notes: BLQ = 200 pg/mL. BLQ concentrations were set to 0. Geometric mean and geometric CV are not presented if any concentrations were BLQ at a particular time point. Presented statistics are based on the PKS and the actual treatment received group.

Source: Table 14.2.3.1

Ranibizumab Concentrations (pg/mL) Time point Statistic	Xlucane N=40	Lucentis N=30
Baseline		
n	38	29
BLQ	38 (100)	28 (96.6)
Mean (SD)	0 (0)	54.8 (295.3)
CV (%)	NA	538.5
Median	0	0
Min, Max	0, 0	0, 1590
Day 1		
n	40	29
BLQ	3 (7.5)	2 (6.9)
Mean (SD)	2230 (1429)	2190 (1336)
CV (%)	64.0	61.2
Median	2180	2370
Min, Max	0, 8060	0, 4780
Week 20		
n	32	24
BLQ	1 (3.1)	0
Mean (SD)	2450 (1384)	2150 (1233)
CV (%)	56.5	57.4
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Min, Max	0, 6350	397, 6170

Abbreviations: BLQ, below the lower limit of quantification; CV, coefficient of variation; Max, maximum; Min, minimum; NA, not applicable; PKS, pharmacokinetic set; SD, standard deviation.
Notes: BLQ = 200 pg/mL. BLQ concentrations were set to 0. Geometric mean and geometric CV are not presented if any concentrations were BLQ at a particular time point. Presented statistics are based on the PKS and the actual treatment received group.
Source: Table 14.2.3.1

To account for potential differences in ranibizumab protein concentration between Ximluci and Lucentis batches, plasma ranibizumab concentrations were normalised for protein concentration. The plasma ranibizumab concentrations normalised for protein concentration were similar between the Ximluci and Lucentis groups at Day 1 and Week 20.

Immunogenicity

292 subjects in the Ximluci group and 289 subjects in the Lucentis group were included in the evaluation of immunogenicity. At baseline, the incidence of positive ADA was 12 subjects (4.2%) in the Ximluci group and 8 subjects (2.9%) in the Lucentis group. At Week 24, the cumulative incidence of positive ADA was low in both treatment groups: 22 subjects (7.5%) in the Ximluci group and 17 subjects (5.9%) in the Lucentis group. At Week 52, the cumulative incidence of positive ADA was 33 subjects (11.3%) in the Ximluci group and 38 subjects (13.1%) in the Lucentis group. There were no notable differences in immunogenicity results between the Ximluci and Lucentis groups over time and the incidence of positive ADA was similar between treatment groups at all assessed time points.

2.4.3. Discussion on clinical pharmacology

Bioanalytical methods

Bioanalytical report PK

The Applicant is employing an ECL immunoassay for the detection and quantitation of Ximluci (ranibizumab) in Human plasma. To do this, 209 samples were collected, however, due to errors which have been sufficiently documented only 205 results are reported.

The calibration standards and QC samples (low mid and high) acceptance criteria have been provided and are in line with the EU guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1). A short description of the run procedure and the run acceptance criteria has been provided. This is deemed appropriate for the assay report. No deviations for the standard operating procedure (SOP) were reported.

The Applicant has confirmed as part of the D120 responses that the samples were stored at -20°C for a maximum of 201 days before transfer to the lab and subsequent storage at -80°C. Updated data has been provided demonstrating that the storage of Ximluci and Lucentis for 9 months (270 days) does not impact quantification of Ximluci. Long-term stability studies are ongoing for plasma stored at -80°C and are anticipated to be completed by H1 2023. The median storage time for samples during this study is 307 days, while one sample has been stored for 691 day. The issue is considered resolved.

Analytical Method Validation PK

The Applicant has provided a validation report outlining the processes employed for the validation of the assay for the quantitation of Ranibizumab biosimilar (Ximluci) and originator (Lucentis®) in human plasma. The assay used for the quantitation of Ranibizumab was electrochemiluminescence (ECL) immunoassay. The steps of the ECL immunoassay have been well described and the method is considered adequate for the quantification of Ranibizumab. A summary of the validation steps has been provided which defines the testing performed and the results obtained.

The run acceptance criteria has been defined for precision and accuracy, specificity, selectivity, dilution linearity and stability. Validation has been performed on the calibration standards and QC samples in accordance with the EU guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1) with the appropriate acceptance standards set and data provided demonstrating they meet these acceptance criteria.

The method has been for the most part validated according to EU guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1), however, a few queries were raised. It is noted that while parallelism acceptance criteria have been set, however, no validation has been performed. It has been stated that due to the lack of highly concentrated clinical samples and the fact that the clinical samples were successfully analysed undiluted, that parallelism is evaluated adequately by selectivity and dilutional linearity which is considered appropriate. Cross validation data has now been provided for a concentration range (200 – 120,000 pg/mL) that shows there is no bias towards either Ximluci or Lucentis as the relative bias (%RE) at nominal concentrations for each data point is less than 15%. It has been confirmed that no specificity testing was done as there was no administration of any co-medication. In addition, the patients enrolled in the study were not allowed receive treatments that might interfere with the assessment of study endpoints.

Bioanalytical Report ADA and NAb

The Applicant has provided data for the detection of anti-drug antibodies (ADA) and neutralising antibodies (NAb) to ranibizumab in human serum. The method has been well described and the results for each patient have been supplied. For the ADA assay, a bridging format was used to determine if anti-ranibizumab antibodies were present in the sample, if samples were found positive in the screening step then a confirmatory assay re-assessed these positive samples through the addition of unlabelled ranibizumab to determine if the assay signal was inhibited. If the samples were deemed positive, a titration assay semi-quantified the antibody response by determining a titre for signal inhibition. All samples confirmed positive in the ADA confirmatory assay were analysed for the presence of NAbs. Overall, the data provided in the report for the ADA and NAb testing is deemed sufficient.

Analytical Method Validation ADA

The Applicant is using a bridging format to determine the presence of anti-ranibizumab antibodies. Data has now been provided to support a minimum required dilution of 1:10.

A screening cut point has been established using a floating cut point approach. In this approach a plate-specific floating cut point approach is being used, this is endorsed. The screening cut point data was generated using 50 lots of healthy human serum as control sera from wAMD patients were not commercially available. Data has been provided which showed that based on the screening factor set from the healthy patients, a FPR of 6.51% for the clinical patients was determined which is close to the ideal value of 5%. The confirmatory cut point has been established using 50 samples with a 1% false positive rate allowed.

Assay precision was performed to determine inter- and intra-assay precision using the positive controls. Inter-assay precision was determined using 5 batches (n=3) and 1 batch (n=6) by 2 analysts on 3 different days using the screening and confirmatory format.

Matrix selectively was performed on non-elderly serum and elderly serum with spiked positive control material. For the non-elderly samples, three PCL-2 samples were below the confirmatory acceptance criteria. The Applicant argues that although two elderly rum samples at the 1.20 ng/mL positive control (PCL-1) showed a % Inhibition ≤ CCP, the acceptance criteria set by the Applicant is more strict than the criteria in the EMA's Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). In addition, following respiking studies using elderly patient serum the results met the companies 90% acceptance criteria for selectivity in elderly serum. It is agreed that the ADA assay meets the method validation acceptance criteria and there is no risk for false negatives.

Further matrix effects by hemolysis and lipemia on detection of anti-Ximluci antibodies in human serum samples were investigated. For both the hemolysed and lipemic serum, several results did not meet the acceptance criteria and therefore the experiment was repeated with the initial 5 serum lots and an additional 5 lots. In the repeated experiment, all results passed for PCH and PCL-1 for the hemolysed samples. For the lipemic samples, 1/10 results failed the confirmatory assay for PCL-1. The Applicant argues that this is just below the target value of 90%. In a post hoc analysis, the Applicant identified patients with triglyceride levels exceeding 3.4 mmol/L as these are considered lipemic. The lipemic sample set confirmed 36.4% ADA-positive samples which was smaller than the overall sample set which had 45.9% ADA-positive samples, however, it is agreed that due to the small sample size it is not possible to conclude if there is a bias for lipemic samples and it can be agreed that it is unlikely there is false-negative results from the analysis of potentially lipemic samples in the ADA confirmatory assay.

No prozone effect was determined using one sample of ultra-high concentration PC stock (107000 ng/mL) prepared in human serum which was diluted 3-fold. Additional data has been provided with the D120 responses that shows the prozone effect was investigated during method development by preparing anti-Ximluci PC and anti-Lucentis PC at a concentration of 26,750 ng/mL and performing serial dilutions 2-fold. The samples were performed in triplicate and the result for each ruled out a prozone effect.

The Applicant argues that the tolerance curves for Ximluci and Lucentis are visually comparable, thereby demonstrating antigenic equivalence and justifying the appropriateness of using a single assay approach. Given the difficulty in drawing a definitive conclusion from this data, the Applicant should provide additional data to justify antigenic equivalence. The Applicant has provided expanded data analysis which studied the antigenic equivalency of Ximluci and Lucentis at concentrations up to 8 µg/mL at two positive control concentrations PC-(H) high and PC-(M) medium. The difference in signal in the presence of Ximluci and Lucentis was shown to be within the validated precision of the assay

(%CV<20%), therefore, it is agreed the method is suitable in detecting ADA towards Ximluci or Lucentis.

No robustness testing has been performed, the Applicant argues that they have demonstrated robustness through the study of accuracy, precision, selectivity, target interference, prozone effect, drug tolerance, one-assay approach short-term stability, and bench stability. It is agreed that the Applicant has shown the method is robust to changes in conditions.

Analytical Method Validation Nab

The Applicant is using an electrochemiluminescence method whereby samples and controls are first incubated with biotinylated Ximluci. The anti-ranibizumab neutralizing antibodies bound to biotinylated Ximluci are captured on a streptavidin-coated ELISA plate. The antibodies are eluted and incubated with ruthenylated Ximluci in a streptavidin plated coated with biotinylated VEGF. The signal generated from reading this plate has an inverse relationship with the level of anti-ranibizumab neutralizing antibodies. It is noted that the minimum required dilution is stated to be 1:2.5, however, no data to support this has been provided, as part of the D120 responses they have shown that at a dilution of 2.5 the method performs adequately in determining the neutralising antibodies using various different reagent concentrations and conditions. In addition, the dilution of 2.5 is considered very low and is at the range that would be expected for this kind of assay. The applicant has confirmed that the CoA for the positive control "Affinity Purified Rabbit Polyclonal IgG antibodies against ranibizumab" is attached in Appendix C of the NAb validation report, however, it is under the name "Affinity Purified Antibody".

A cut point factor for the neutralising assay was determined using 50 lots of human serum from healthy subjects over 4 days by 2 analysts. A justification has been provided to state healthy serum was chosen as wAMD patients were not commercially available. A floating cut point was used for the assay, this is endorsed. Specificity testing data was provided to show the assays ability to detect neutralising antibodies in the presence healthy human serum and elderly human serum. In addition, the Applicant showed that increasing amounts of Ximluci or Lucentis in the presence of the PC could inhibit the assay signal, demonstrating the response is specific for NAb towards the drug product. Assay precision was performed to determine inter- and intra-assay precision using the positive controls. All the samples met the acceptance criteria for the inter- and intra-assay precision.

Drug tolerance studies determined that the NAb assay is tolerant of up to 5.00 ng/mL Ximluci at the PCL (245 ng/mL) level and up to 10.0 ng/mL of Ximluci at the PCM (600 ng/mL) and PCH (4000 ng/mL) antibody levels. The assay is tolerant of up to 10.0 ng/mL of Lucentis at the PCL (245 ng/mL), PCM (600 ng/mL) and PCH (4000 ng/mL) antibody levels. The Applicant states the potential of free drug interference with immunogenicity testing was factored into the design of the sampling strategy of study XBR1001. For the PK study, samples were collected 23h (+/- 60 minutes) after initial dosing and 23h (+/- 60 minutes) after the sixth dose (week 20) which ensures the PK measurements are near the Cmax, however, for the immunogenicity testing sampling was done immediately before initiation of the next treatment cycle which ensures the least drug interference with ADA detection.

No robustness testing has been performed, however, it is agreed that robustness shown as the method was developed and validated at a central bioanalysis laboratory and the following parameters were validated; cut point factor determination, sensitivity, precision, matrix selectivity, drug tolerance, stability, prozone effect, short-term stability, control response ranges, and bench stability. In addition, no long-term stability data has been provided, however, it is agreed that the Applicant does not need to provide long-term stability data for the ADA/NAb as previous scientific studies have shown that neutralising antibodies are stable for several years.

Biosimilarity

The Phase 3 study (XBR1001, Xplore) comparing Ximluci to EU-Lucentis in patients with wAMD included a PK sub-study for assessment of similarity in systemic exposure between Ximluci vs. EU-Lucentis. The design and methodology of this sub-study are considered acceptable. The systemic exposure and immunogenicity of ranibizumab appear similar between the Ximluci and Lucentis groups in this study, which provides support for clinical similarity between Ximluci vs Lucentis.

No other clinical PK studies or analyses, including plasma protein binding, hepatic metabolism, special populations, drug-drug interactions and other intrinsic and extrinsic PK factors, were performed and no specific clinical pharmacodynamic studies were performed. This is acceptable for this biosimilar application since it relies on the information already known of the reference product.

2.4.4. Conclusions on clinical pharmacology

Only one clinical study was conducted to support approval of the biosimilar product Ximluci, which included a PK sub-study. This is considered sufficient for the present application. There were no major objections raised for clinical pharmacology. Some other concerns were raised and all of these have been sufficiently resolved.

2.4.5. Clinical efficacy

The applicant has submitted one randomised double-blind study comparing the ranibizumab biosimilar (Ximluci) with the authorised reference product Lucentis in patients with wet age-related macular degeneration.

The study was carried out at a number of centres in the EU as well as in the USA, India, Israel, Russia, and Ukraine. The study is 52 weeks in duration. .

A number of scientific advices' were provided by the CHMP in relation to the study design. In the main, the Applicant followed the scientific advice.

2.4.5.1. Main study

Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Xlucane* versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration (XBR1001)

*Xlucane was an earlier name for Ximluci

Methods

This was a 52 week randomised double-blind controlled study to compare the efficacy and safety of Ximluci (Xlucane) to Lucentis in patients with neovascular also known as wet age related macular degeneration. When all subjects completed their 6-month assessments, an analysis of efficacy and safety endpoints, as well as PK and immunogenicity, was performed. The analysis did not affect further conduct of the study. The subjects, masked investigators, and study personnel remained masked to the treatment group assignment throughout the study period after randomisation. The analysis was reported in an Interim Analysis CSR (dated 13 August 2021). The Interim Analysis CSR (Through Week 24), dated 13 August 2021, presented study results for all subjects through the Week 24 visit and included data up to the interim analysis data snapshot of 10 June 2021 for all subjects in the study.

The Final CSR (Through Week 52) included all data collected in the study up to the Week 52 End of Treatment Visit (11 November 2021).

Study Participants

The study population included patients with newly diagnosed active wet AMD who met the inclusion criteria and did not meet the exclusion criteria listed below.

Inclusion Criteria

To be eligible for study entry, subjects had to satisfy all of the following inclusion criteria:

1. Written and signed informed consent form obtained at screening before any study related procedures are performed. Patients must be capable of providing their own consent (an impartial witness must be present in case of illiterate patients).
2. Willingness and ability to undertake all scheduled visits and assessments as judged by the investigator.
3. Newly diagnosed, active subfoveal choroidal neovascularization (CNV) lesion secondary to age-related macular degeneration (AMD) in the study eye. Note: active CNV indicates the presence of leakage as evidenced by fluorescein angiography (FA) and intra- or subretinal fluid as evidenced by optical coherence tomography (OCT), which must be confirmed by the central reading center during Screening:
    a. The area of CNV must be ≥ 50% of the total lesion area in the study eye, and
    b. Total lesion area ≤ 9.0 disc areas (DA) in size (including blood, scars, and neovascularization) as assessed by FA in the study eye.
4. BCVA of ≤ 73 and ≥ 49 Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in the study eye using the ETDRS chart (20/40 to 20/100 Snellen equivalent) at Screening.
5. Fellow eye should not be expected to need any anti-vascular endothelial growth factor (VEGF) treatment for the duration of study participation based on
6. Investigator's decision.
7. Age ≥ 50 years at screening.
8. Male and female subjects of childbearing potential must be willing to completely abstain or agree to use an appropriate method of contraception from the time of signing informed consent form and for the duration of study participation through 3 months after the last dose of study drug.
    a. A woman of childbearing potential is any woman, regardless of sexual orientation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
    b. A man of sexual potential is any man who has not been surgically sterilized (eg, has not undergone bilateral orchiectomy).

Exclusion Criteria

Subjects were excluded from the study if **1 or more** of the following exclusion criteria was applicable:

1. Any previous intervention, including pharmacological treatment, laser, and/or surgery for wAMD in either eye; (exception: vitamin supplementation for AMD prevention). In cases of

end stage wAMD in the fellow eye where anatomical and functional status diagnosed at Screening disqualified a subject from IVT anti-VEGF treatment according to local medical standards of care, the previous laser photocoagulation or photodynamic therapy procedure in fellow eye performed for wAMD treatment was allowed. This criterion did not apply to the fellow eye, in cases of subjects who had only 1 eye or the fellow eye fulfilled additional criteria specified in protocol Section 8.3.4.

2. Any previous vitreoretinal surgery in the study eye for any cause.
3. Any previous IVT treatment, including any anti-VEGF medications, steroids, and/or any other investigational medication in either eye.
4. The use of long-acting steroids, either systemic or intraocular in any eye, in the 18 months before planned initiation of study treatment. Note: Current or planned Iluvien® (fluocinolone acetonide IVT) implantation during the study was prohibited.
5. Subfoveal fibrosis, subfoveal atrophy, and/or scarring extending >50% of total lesion area in the study eye assessed by the investigator at Screening and confirmed by the CRC prior to Randomisation.
6. Choroidal neovascularisation in either eye due to non-AMD causes (e.g., diabetic macular oedema, retinal vein occlusion, ocular histoplasmosis, trauma) assessed by FA and confirmed by CRC. This criterion was not applicable for the fellow eye, in cases of subjects who had only 1 eye or the fellow eye optical media opacity which prevented taking the FA/OCT/FP images and the fellow eye fulfilled additional criteria specified in protocol Section 8.3.4.
7. Active or recent (within 28 days prior to Randomisation) intraocular, extraocular, and periocular inflammation or infection in either eye.
8. History of idiopathic or autoimmune-associated uveitis in either eye.
9. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
10. Unmedicated intraocular pressure (IOP) ≥30 mmHg at Screening in either eye.
11. Topical ocular corticosteroids administered for ≥30 consecutive days in the study eye within 90 days before Screening.
12. Spherical equivalent of the refractive error in the study eye that demonstrated more than 8 diopters of myopia.
13. Corneal transplant or corneal dystrophy in the study eye.
14. History of rhegmatogenous retinal detachment in the study eye.
15. History of macular hole in the study eye.
16. Retinal pigment epithelial tear or rip involving the macula in the study eye assessed by FA and confirmed by the CRC.
17. Current vitreous haemorrhage in the study eye.
18. Subretinal haemorrhage that was ≥50% of the total lesion area in the study eye, or if the subretinal haemorrhage that involved the fovea was 1 or more disc areas (≥2.54 mm^2) in size in the study eye, as assessed by FA and confirmed by the CRC.
19. Other intraocular surgery (including cataract surgery) in the study eye within the 3 months prior to Baseline. The yttrium aluminium garnet (YAG) posterior capsulotomy was allowed

no later than 4 weeks prior to Screening.

20. Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, required treatment during the study period to prevent or treat loss of visual acuity.
21. Significant media opacities (including cataract) in the study eye which interfered with BCVA assessment or fundus imaging (FA/fundus photography/OCT).
22. Aphakia or absence of the posterior capsule in the study eye, unless it occurred as a result of a YAG posterior capsulotomy in association with prior posterior chamber intraocular lens implantation.
23. Presence of advanced glaucoma or optic neuropathy that involved or threatened the central visual field in the study eye (as judged by the investigator).
24. History of glaucoma filtering surgery or argon laser trabeculoplasty in the study eye (exception: Laser iridotomy and selective laser trabeculoplasty were allowed).
25. Uncontrolled ocular glaucoma or hypertension in the study eye, defined as IOP ≥25 mmHg despite treatment with anti-glaucoma medication.
26. Any previous systemic anti-VEGF treatment (eg, bevacizumab).
27. Contraindication for Lucentis (hypersensitivity to ranibizumab or to any of the study treatment excipients).
28. Current treatment for active systemic infection.
29. Females who were pregnant, nursing, planning a pregnancy during the study, or of childbearing potential and not using a reliable method of contraception and/or unwilling to use a reliable method of contraception during their participation in the study. Women of childbearing potential at the Screening Visit (prior to treatment) must have had a negative pregnancy test to receive study medication.
30. Participation in another clinical trial within the previous 3 months or any other clinical trial of anti-angiogenic drugs.
31. Reasonable suspicion of other disease or condition that rendered the subject at a high risk of treatment complications or otherwise confounded interpretation of the study results (as judged by the investigator).
32. *PK subgroup only*: Contraindication for additional blood sampling (as judged by the investigator).

Treatments

Ximluci 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) was administered by ophthalmic IVT injection (only) once every 4 weeks (approximately 28 days/monthly) in the study eye for 12 months in subjects with wAMD who were randomised to receive Ximluci.

Lucentis 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) was also administered by ophthalmic IVT injection (only) once every 4 weeks (approximately 28 days/monthly) in the study eye for 12 months in subjects with wAMD who were randomised to receive Lucentis.

Objectives

The primary objective of the study was to demonstrate that the biosimilar candidate Ximluci is equivalent to Lucentis in subjects with wAMD as assessed by the change in best corrected visual acuity (BCVA) from Baseline to Week 8.

Relevant secondary objectives of the study were as follows:

- To evaluate the efficacy of Ximluci versus Lucentis in subjects with wAMD based on central foveal thickness (CFT) measured by spectral domain optical coherence tomography (OCT), area of choroidal neovascularisation (CNV), and presence of leakage assessed by fundus fluorescein angiography (FA)
- To evaluate the safety of Ximluci versus Lucentis
- To evaluate the systemic exposure of Ximluci versus Lucentis in subjects participating in PK evaluation
- To evaluate immunogenicity (ie, anti-ranibizumab antibodies and neutralising anti-ranibizumab antibodies) of Ximluci versus Lucentis

The study is an equivalence study. To test for equivalence between the 2 treatments, a two 1-sided testing procedure was used to test each of the following hypotheses using 1-sided tests at the 5% (United States) and 2.5% ROW significance levels:

a) H0,A: μXimluci - μLucentis ≤ -3.5 versus H1,A: μXimluci - μLucentis > -3.5

b) H0,B: μXimluci - μLucentis ≥ 3.5 versus H0,B: μXimluci - μLucentis < 3.5

with μ = mean change in BCVA letters at Week 8 compared to Baseline using the ETDRS protocol for the identified treatment group.

Biosimilarity was to be concluded if the 2-sided 90% (US FDA) or 95% (Rest of the World) confidence interval (CI) for the difference in mean change in BCVA at Week 8 between Ximluci and Lucentis was confined within the equivalence margin of ±3.5 letters. A meta-analysis of ANCHOR and MARINA studies was done in order to focus on Week 8 BCVA data and ensure that the proposed equivalence margin would preserve at least 50% of the lower limit of the 95% CI for the difference in mean change in BCVA between treatment and placebo which was 7.7 letters. Considering this and that the minimal clinically important difference in visual acuity had previously been set to or estimated to be 5 to 10 letters, an equivalence margin of ±3.5 letters was deemed adequate and supported by EMA/FDA in recent scientific advice.

Due to the increase in protocol deviations (PDs) related to the COVID-19 pandemic and following the recent ICH E9 (R1) Addendum, an estimand framework was provided in the protocol to provide a more comprehensive approach to show the impact of COVID-19 in the analysis. For the primary estimand, the scientific question of interest was the between-group difference (Ximluci versus Lucentis) in the mean change from Baseline in BCVA letter score at Week 8 in subjects who fulfilled the study eligibility criteria, had no IEs up to and including the Week 8 BCVA assessment, and completed 8 weeks of treatment of study drug (given as a single ophthalmic IVT injection every 4 weeks/monthly).

IEs were defined as:

- Early discontinuation of study treatment. Subsequent data (missing or collected) were imputed in the analysis with a hypothetical strategy.
- Non-adherence with the protocol which would potentially affect the efficacy results. Such identified data (missing or collected) were imputed in the analysis with a hypothetical strategy.
- Start of anti-VEGF treatment in the fellow eye prior to the Week 8 analysis visit. Subsequent

data (missing or collected) were imputed in the analysis with a hypothetical strategy.

The secondary estimand of the study for the primary endpoint was meant to use a strategy to address the IEs compared to the primary estimand: a treatment policy implemented by using any data collected following the IE in the analysis. So the scientific question of interest was the between-group difference (Ximluci versus Lucentis) in the mean change from baseline in BCVA letter score at Week 8 in subjects who fulfilled the study eligibility criteria and completed 8 weeks of treatment of study drug, regardless of any other IEs. However, because the study design did not plan for assessments following early treatment discontinuation, it was not possible to apply a true treatment policy strategy. As such, any missing data following early treatment discontinuation was imputed in line with a hypothetical strategy.

Outcomes/endpoints

The primary endpoint of the study was the change in BCVA letters at Week 8 compared to Baseline using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol for the study eye.

The secondary endpoints of the study were as follows:

- Change in BCVA letters at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 52 compared to Baseline using the ETDRS protocol for the study eye
- Change in total size of choroidal neovascular leakage area in the study eye measured by FA at Week 24 and Week 52 compared to Baseline
- Change in total size of CNV in the study eye measured by FA at Week 24 and Week 52 compared to Baseline
- Change in CFT in the study eye measured by OCT at Week 2, Week 4, Week 8, Week 16, Week 24, Week 36, and Week 52 compared to Baseline
- Changes in the size and/or number of intraretinal cystoid space (cysts), subretinal fluid, and retinal pigment epithelium detachments in the study eye measured by qualitative morphology-based OCT compared to Baseline
- Percentage of subjects with loss of <15 letters using ETDRS, evaluated as change at Week 4, 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 4, Week 8, Week 24, and Week 52 compared to Baseline in the study eye
- Percentage of subjects without intra- or subretinal fluid in the study eye (ie, completely dry) at Week 24 and Week 52
- Percentage of subjects with retinal pigment epithelium detachments in the study eye

Sample size

The change in BCVA after 8 weeks was evaluated from previous studies based on similar patient populations. There was a wide range of SD across the studies, ranging from 8.58 letters to 11.83 letters.

For the purpose of sample size calculation, an SD of 10 letters was assumed for this study. This was based on an analysis of the data from clinical trials of the originator product demonstrating a clear correlation between Baseline BCVA and the SD of the change of BCVA at Week 8.

Considering that a narrower inclusion criterion for BCVA was being applied in this study compared to the studies of the originator product, it was expected that a Baseline BCVA of around 60 letters would be observed. Therefore, an SD of 10 for the primary endpoint was well in the upper range of what was expected.

From 580 randomised subjects, there would be >90% power to show equivalence (ie, 2-sided 95% CI for the mean difference between Ximluci and Lucentis would be confined within the equivalence margin of ±3.5 letters) if the SD was no more than 10.

Randomisation and Blinding (masking)

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

The randomisation scheme automatically ensured that the study drug assignment for a given subject was random and that an overall 1:1 ratio of assignments to each of the 2 study drug treatments was approximated.

Randomisation was stratified according to the following: eye colour (light iris versus dark iris), geographical region where enrolled, and the BCVA letters at Baseline (55 or lower, 56 to 65, 66 or higher). Permuted random blocks within each stratification combination was used to ensure the 1:1 ratio within each combination.

An independent biostatistician created the randomisation scheme, which remained unavailable to all other masked individuals, until after study completion and subsequent locking of the study database.

Once a randomisation number had been assigned, that number must not have been used again for any other subject.

The study was double masked. The identity of the study treatment assignments were not known to subjects.Those involved in the preparation or administration of the study treatments were not involved in the assessment of efficacy. Randomisation information for any particular subject was 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 participant.

When all subjects completed their 6-month assessments, an unmasked analysis of efficacy (i.e. equivalence) and safety endpoints, as well as PK and immunogenicity, was performed. The aim of the unmasked analysis was to initiate the submission of the application for marketing authorisation as agreed with the EMA. The analysis was reported in an Interim Analysis CSR (dated 13 August 2021). The Interim Analysis CSR (Through Week 24), dated 13 August 2021, presented study results for all subjects through the Week 24 visit and included data up to the interim analysis data snapshot of 10 June 2021 for all subjects in the study. The Final CSR (Through Week 52) included all data collected in the study up to the Week 52 End of Treatment Visit (11 November 2021).

Statistical methods

The change in BCVA letters at Week 8 compared to Baseline using the ETDRS protocol in the study eye was analysed using a mixed model for repeated measures (MMRM) on evaluable data for the primary analysis of the primary estimand of the study.

An MMRM was implemented in SAS PROC MIXED using a restricted maximum likelihood approach. An unstructured covariance structure shared across treatment groups was used to model the within-

subject errors (UN option in PROC MIXED). If the model failed to converge, a heterogeneous Toeplitz structure (TOEPH option in PROC MIXED) was used. If the model still failed to converge, the compound symmetry structure (CS option in PROC MIXED) was used. The Kenward-Rogers correction to degrees of freedom was applied (DDFM=KR option in PROC MIXED). The least square (LS) means (and standard errors [SEs]) for each treatment as well as the treatment difference from the model at Week 8 were presented along with the 90% and 95% 2-sided CIs. To prove the 2 products to be biosimilar, the confidence limits for the LS means difference had to be within the equivalence margin of 3.5 letters at Week 8 (90% CI for United States and 95% CI for ROW).

Results

Participant flow

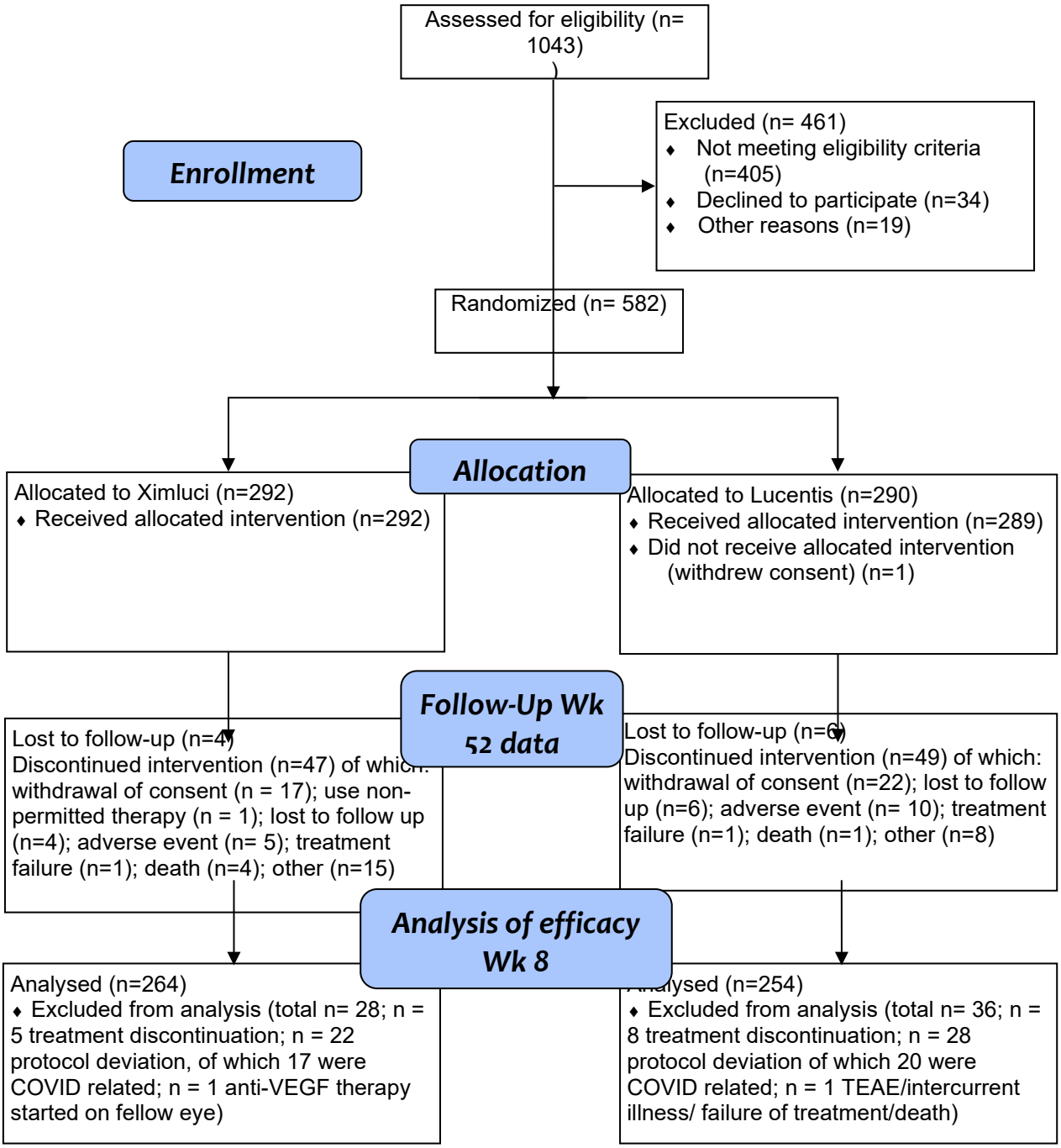
One thousand and forty-three patients were screened for eligibility of whom 582 were randomised 292 to the Ximluci arm and 290 to the Lucentis arm. All patients randomised to Ximluci arm and 289 patients randomised to Lucentis were dosed.

The primary endpoint was evaluated at Week 8 by which time there were 5 (1.7%) treatment discontinuations from Ximluci and 8 (2.8%) from Lucentis.

At week 52 a total of 96 subjects (16.5%) discontinued the study treatment early, including 47 subjects(16.1%) in the Ximluci group and 49 subjects (16.9%) in the Lucentis group. The most common
reason for early discontinuation of study treatment in both groups was subject request (ie, withdrawal of consent).

The primary endpoint was evaluated at Week 8 by which time there were 4 (1.4%) treatment discontinuations from Ximluci and 6 (2.1%) from Lucentis.

Figure 1



Recruitment

The first subject was screened on 09 April 2019. The date of the interim analysis snapshot was 10 June 2021. The date of last observation (Last Subject Last Visit) was 11 November 2021.

The majority of subjects were recruited from Europe (72.9%), followed by Asia (14.2%), and the United States (12.9%).

Conduct of the study

The original protocol (version 1.0, dated 02 November 2018), was amended 4 times. The most relevant amendments are those for Amendments 3, 4 and 5, which are summarised below.

Protocol Amendment 3, Version 1.0 (dated 06 May 2020)

- Clarification around equivalence margin of ±3.5, as agreed with the EMA/FDA.
- Updated the PK substudy sample size from 60 to between approximately 40 to 60 subjects based on ongoing discussion with the EMA due to the increased risk of COVID-19 exposure during the COVID-19 pandemic in connection to additional visits that the PK substudy mandates.
- Clarification added to exclusion criteria 1 and 6 to explain non-applicable circumstances due to medical condition of the fellow eye, in cases where a subject had only 1 eye or their fellow eye fulfilled additional criteria (as specified).
- Clarification to exclusion criterion 5 to exclude subfoveal fibrosis, subfoveal atrophy, and/or scarring extending >50% of total lesion area in the study eye as assessed by the investigator at screening and confirmed by the CRC prior to Randomisation; change was implemented throughout the protocol.
- Addition of text regarding the difference in approach around the CI used for evaluation of study results between the United States (90% CI) and ROW (95% CI) as agreed upon with the relevant regulatory authorities; change was implemented throughout the protocol.
- The interim analysis at Month 2 was removed following additional discussions with the EMA, as the agency felt this analysis could potentially jeopardise the integrity of the study.
- Clarification that subjects with only 1 eye or fellow eye with opaque optical media opacity can be considered for study participation by the investigator under specific circumstances.
- Clarification added to the statistical methods section as to how the data will be handled due to the COVID-19 pandemic.

Protocol Amendment 4, Version 1.0 (dated 26 November 2020)

Due to the high number of PDs related to the COVID-19 pandemic, the strategy for the efficacy analyses was updated to be more in line with the ICH E9 Addendum estimand approach. The definitions of the primary efficacy estimand and IEs were added and it was stated that this will be the primary assessment of biosimilarity.

- Removal of the per-protocol set, adding that all efficacy analyses will use the FAS using estimand methodology. The review of IEs as part of the blinded data review meeting including the PDs related to COVID-19 was detailed.
- Clarification regarding the missing data assumptions relating to primary and sensitivity analyses for each endpoint/estimand. Added a statement that primarily, COVID-19 related missing data will be treated as MAR.
- Updated the analysis of response endpoints using the Miettinen-Nurminen method rather than the Newcombe.

Protocol Version Amendment 5, Version 1.0 (dated 24 February 2021)

- Clarification regarding the maintenance of masking in connection to the interim analysis. Text was added to clarify that subject treatment assignments will not be revealed in connection to the interim analysis and thereby the masking of the study will be maintained.

- Central provision of BD needles and syringes was suspended until further notice, per company decision.

Protocol deviations

The number of subjects who had at least 1 major protocol deviation was balanced across both treatment groups. In the Ximluci group, 131 subjects (44.9%) had 257 major PDs. In the Lucentis group, 133 subjects (45.9%) had 267 major PDs. The most common major PDs in both groups were related to missed visits: "COVID-19 – missed visit" (16.1% of subjects in the Ximluci group and 15.9% of subjects in the Lucentis group) and "procedure not per protocol – missed (omitted) assessment" (12.7% of subjects in the Ximluci group and 13.1% of subjects in the Lucentis group).

A total of 16 subjects (5.5%) in the Ximluci group and 6 subjects (2.1%) in the Lucentis group had a major PD in the category of "stratification error". All of these stratification errors were related to the BCVA letters at Baseline group (55 letters or lower, 56 to 65 letters, 66 letters or higher), where the site inadvertently entered the incorrect Baseline BCVA stratification group at the Randomisation visit; however, these deviations did not impact the overall balanced distribution of assignment to the 2 treatments by Baseline BCVA group (see Section 10.4.1). An additional 3 subjects (2 subjects in the Ximluci group and 1 subjects in the Lucentis group) had similar stratification errors related to the site entering the incorrect Baseline BCVA stratification group, but these were not recorded as major PDs under the category of "stratification error." The subgroup analysis of BCVA letters at Baseline used the actual BCVA value at Baseline; therefore, the stratification errors, which were human errors at the site, did not have an impact on the subgroup analysis of the primary endpoint by Baseline BCVA category.

The number of subjects who had at least 1 major PD in relation to COVID-19 was balanced across both treatment groups. In the Ximluci group, 63 subjects (21.6%) had 127 major PDs in relation to COVID-19. In the Lucentis group, 62 subjects (21.4%) had 123 major PDs in relation to COVID-19. . Major PDs in relation to COVID-19 included missed visits (16.1% of subjects in the Ximluci group and 15.9% of subjects in the Lucentis group), study procedure not performed per protocol (4.5% of subjects in the Ximluci group and 6.6% of subjects in the Lucentis group), visit out-of-window (1.4% of subjects in the Ximluci group and 1.0% of subjects in the Lucentis group), and "other" COVID-related PDs (2.7% of subjects in the Ximluci group and 0.7% of subjects in the Lucentis group).

Baseline data

The demographics and baseline characteristics were well balanced across the Ximluci and Lucentis treatment groups. The mean age of subjects in the Ximluci group was 74.5 (8.68) years and 73.8 (8.25) years in the Lucentis group. The majority of subjects (44.2%) in both groups were were in the 70 to 79 years age group, followed by 27.7% of subjects in the 80+ years age group and 23.4% in the 60 to 69 years age group. There was a slightly higher proportion of subjects in the 80+ years age group in the Ximluci group (31.2%) compared to the Lucentis group (24.1%).

Just over half of the subjects were female, 57.5% in the Ximluci group and 54.1% in the Lucentis group. Just over 70% were recruited from Europe, 72.6% in the Ximluci and 73.1% in the Lucentis group.

The distribution of category of baseline visual acuity was also similar across treatment groups. Approximately 26% in both treatment arms had a baseline BCVA of 55 or less letters. Thirty six percent of those treated with Ximluci and 34.5% of those treated with Lucentis had a BCVA of 56 to 65 letters. Thirty seven point seven percent in the Ximluci arm and 39% in the Lucentis arm had a BCVA of 66, or higher letters.

Table 4: Demographics and Baseline Characteristics (Full Analysis Set)

Baseline Variable **Statistic/Category**	**Ximluci** **N=292**	**Lucentis** **N=290**
Mean Age (SD)	74.5 (8.68)	73.8 (8.25)
Age-group		
50-59	18 (6.2%)	10 (3.4%)
60-69	59 (20.2%)	77 (26.6%)
70-79	124 (42.5%)	133 (45.9%)
80+	91 (31.2%)	70 (24.1%)
Gender		
Female	168 (57.5%)	157 (54.1%)
Male	124 (42.5%)	133 (45.9%)
Geographic region		
Europe	212 (72.6%)	212 (73.1%)
Asia	43 (14.7%)	40 (13.8%)
America	37 (12.7%)	38 (13.1%)
BCVA letter at baseline		
≤ 55	77 (26.4%)	77 (26.5%)
56-65	105 (36%)	100 (34.5%)
≥ 66	110 (37.7%)	113 (39%)
Eye colour		
Dark iris	140 (47.9%)	139 (47.9%)
Light iris	152 (52.1%)	151 (52.1%)
Duration of wAMD in the Study Eye (months)		
Mean (SD)	2.14 (8.255)	1.32 (4.134)
Presence of wAMD in the Fellow Eye, n (%)	28 (9.6)	28 (9.7)
Duration of wAMD in the Fellow Eye (months)		
Mean (SD)	12.80 (21.117)	33.03 (53.008)

Numbers analysed

The Full Analysis Set (FAS) included all subjects for whom treatment regimen was assigned. The FAS was used for all analyses of efficacy endpoints. Subjects were analysed according to the randomised treatment. The full analysis set and the numbers of subjects with evaluable data by timepoint are shown in Table 5.

Table 5: Full analysis set and number of evaluable patients by time point for Ximluci and Lucentis

	Ximluci	Lucentis
Full analysis set	292	290
Number with evaluable data Week 4	276/292	276/290
Number with evaluable data Week 8 (Primary endpoint) *	**264/292**	**254/**290
Number with evaluable data Week 12	259/292	247/290
Number with evaluable data Week 16	242/292	234/290
Number with evaluable data Week 24	239/292	229/290
Number with evaluable data Week 36	223/292	234/290
Number with evaluable data Week 52	212/292	204/290

*Note 278 had a study visit at week 8 in the Ximluci arm and 268 had a study visit in the Lucentis arm.

Outcomes and estimation

Primary efficacy endpoint

The primary endpoint of the study was the change in BCVA letters at Week 8 compared to Baseline using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol for the study eye.

Descriptive statistics

At Baseline, the mean BCVA score was 61.7 letters in the Ximluci group and 61.5 letters in the Lucentis group. Subjects in both the Ximluci group and the Lucentis group responded well to treatment over the 52 weeks of the study based on the observed improvements in visual acuity. At Week 52, the mean BCVA score was 69.3 letters in the Ximluci group and 70.7 letters in the Lucentis group. Small numerical differences in BCVA letter scores (by approximately 1 to 2.5 letters) were observed across the groups over the visits (Table 6) Given the lack of directional consistency of the observed numerical difference with the anatomical endpoints, this was concluded not to be due to any structural differences between the products.

Table 6: BCVA Letter Score in the Study Eye – Descriptive Statistics (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

BCVA Letter Score (Letters) **Time point** **Statistic**	**Ximluci** **N=292**	**Lucentis** **N=290**
Baseline (n) Mean (SD)	292 61.7 (8.11)	290 61.5 (8.20)
Week 4 (n) Mean (SD)	276 66.5 (9.90)	276 67.0 (9.71)
Week 8 (n) Mean (SD)	264 66.8 (11.43)	254 68.7 (9.90)
Week 12 (n) Mean (SD)	259 67.4 (11.18)	247 69.1 (11.06)
Week 16 (n) Mean (SD)	242 68.3 (11.29)	234 69.9 (10.93)
Week 24 (n) Mean (SD)	239 68.6 (12.93)	230 70.4 (11.47)
Week 36 (n) Mean (SD)	223 69.1 (12.49)	234 70.8 (12.41)
Week 52 (n) Mean (SD)	212 69.3 (13.56)	204 70.7 (13.05)

Primary endpoint analysis

The primary analysis (MMRM, evaluable data for primary estimand analyses, with missing data assumed to be missing at random) for the change from Baseline in BCVA letter score in the study eye for the FAS at Week 8, showed that the LS means (SE) change from Baseline in BCVA was 4.57 (0.527) letters in the Ximluci group and 6.37 (0.537) letters in the Lucentis group. The LS means (SE) difference for Ximluci versus Lucentis was -1.79 (0.684) letters and the LS means difference 95% CI was -3.14 to -0.45 which was within the equivalence margin of -3.5 to 3.5 letters (Table 7).

Table 7: Change from Baseline in the BCVA Letter Score in the Study Eye – Primary Analysis MMRM (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

Time point **Statistic**	**Model effects (p-value)**	**Ximluci** **N=292**	**Lucentis** **N=290**
Week 8 LS Means (SE) 95% CI LS Means Diff (95% CI)		4.57 (0.527) 3.54 to 5.61	6.37 (0.537) 5.31 to 7.42 -1.79 (-3.14, -0.45) 0.009
Model effects (p-value)			
Treatment	0.0135		
Baseline BCVA Letters	0.001		
Geographical Region	0.008		
Eye Colour	0.297		
Visit	0.011		
Treatment-by-Visit Interaction	0.317		
Baseline BCVA Letters-by-Visit Interaction	0.034		

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; FAS, full analysis set; IE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error. Notes: The objective of the primary estimand analysis was to estimate the treatment differences under the scenario of no IEs. Only evaluable data were included in this analysis. No data were imputed prior to analysis but the MMRM analysis employs a hypothetical strategy, assuming that non-evaluable and missing data due to IEs are missing at random. P-values for LS mean differences are 2-sided and test for non-zero difference between the treatments. Presented statistics are based on the FAS and the randomised treatment.

Sensitivity analyses of the primary efficacy endpoint (primary estimand analysis)

Sensitivity analyses were performed to assess the impact of missing data assumptions using an ANCOVA model.

A sensitivity analysis using ANCOVA by week for change from Baseline in the BCVA letter score in the study eye (evaluable data for primary estimand analyses) for the FAS showed similar results to the MMRM analysis. At Week 8, the LS means (SE) difference for Ximluci versus Lucentis was -1.7 (0.70) with 95% CI from -3.1 to -0.4 letters for data missing completely at random (MCAR) and also for data missing not at random (MNAR) (Table 8).

Table 8: Change From Baseline in the BCVA Letter Score in the Study Eye – Sensitivity Analyses Using ANCOVA by Week (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

	MCARa			**MNARb**		
Time point **Statistic**		**Ximluci** **N=292**	**Lucentis** **N=290**		**Ximluci** **N=292**	**Lucentis** **N=290**
Week 8						
LS Means (SE)		4.76 (0.603)	6.54 (0.621)		4.63 (0.582)	6.42 (0.598)
95% CI		3.6 to 6.0	5.32 to 7.76		3.49 to 5.77	5.25 to 7.59
LS Means Diff (95% CI)			-1.78 (-3.16, -0.40)			-1.79 (-3.14, -0.44)
P value			0.012			0.010
Model effects (p-value) Treatment Baseline BCVA Letters Geographical Region Eye Colour	0.012 0.002 0.084 0.935					

Abbreviations: ANCOVA, analysis of covariance; BCVA, best corrected visual acuity; CI, confidence interval; FAS, full analysis set; IE, intercurrent event; LS, least squares; MCAR, missing completely at random; MNAR, missing not at random; NA, not applicable; SE, standard error.

a No data are imputed.

b Missing data are multiply imputed using a defined Pattern Mixture Model as per the Statistical Analysis Plan employing a hypothetical strategy. Subjects with data MNAR are assumed to return to an average baseline level that is observed in this population. Otherwise data are multiply imputed assuming data are missing at random. Notes: The objective of the primary estimand analysis was to estimate the treatment differences under the scenario of no IEs. Evaluable data is any data collected that was not impacted by an IE. Only evaluable data are included in these analyses. Separate ANCOVA models were performed for each visit. P-values for LS mean differences are 2-sided and test for non-zero difference between the treatments. Presented statistics are based on the FAS and the randomised treatment.

A further sensitivity analysis using ANCOVA by week for change from Baseline in the BCVA letter score in the study eye (evaluable data for primary estimand analyses) using BOCF and LOCF for the FAS showed similar results (Table 9). At Week 8, the LS means (SE) difference for Ximluci versus Lucentis was -1.5 (0.67) letters for both missing and non-evaluable data imputed using BOCF and imputed using LOCF. The LS means difference 95% CI were both within the equivalence margin of -3.5 to 3.5 letters.

Table 9: Change From Baseline in the BCVA Letter Score in the Study Eye – Further Sensitivity Analysis Using ANCOVA by Week (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

	BOCFa			**LOCFb**		
Time point **Statistic**		**Ximluci** **N=292**	**Lucentis** **N=290**		**Ximluci** **N=292**	**Lucentis** **N=290**
Week 8 LS Means (SE) 95% CI LS Means Diff (95% CI) P value		4.39 (0.571) 3.27 to 5.52	5.94 (0.58) 4.80 to 7.07 -1.54 (-2.86, -0.22) 0.022		4.71(0.572) 3.6 to 5.8	6.20 (0.578) 5.06 to 7.33 -1.49 (-2.81, -0.17) 0.027
Model effects (p-value) Treatment Baseline BCVA Letters Geographical Region Eye Colour	 0.022 <0.001 0.021 0.987			 0.027 0.001 0.069 0.861		

a Missing and non-evaluable data are imputed using BOCF.

b Missing and non-evaluable data are imputed using LOCF.

Notes: The objective of the primary estimand analysis was to estimate the treatment differences under the scenario of no IEs. Evaluable data is any data collected that was not impacted by an IE. Only evaluable data are included in these analyses. Separate ANCOVA models were performed for each visit. P-values for LS mean differences are 2-sided and test for non-zero difference between the treatments. Presented statistics are based on the FAS and the randomised treatment.

The primary efficacy analysis was repeated using the evaluable data for the primary analysis of the secondary estimand of the study The results for the secondary estimand analysis were similar to the primary estimand results (Table 10).

Table 10: Change from Baseline in the BCVA Letter Score in the Study Eye – Primary Analysis MMRM (Observed Data for Secondary Estimand Analyses) (Full Analysis Set)

Time point **Statistic**	**Model effects (p-value)**	**Ximluci** **N=292**	**Lucentis** **N=290**
Week 8 LS Means (SE) 95% CI		4.37 (0.543) 3.30 to 5.44	5.87 (0.551) 4.79 to 6.95

LS Means Diff (95% CI) P value			-1.5 (-2.87, -0.14) 0.031
Model effects (p-value) Treatment Baseline BCVA Letters Geographical Region Eye Colour Visit Treatment-by-Visit Interaction Baseline BCVA Letters-by-Visit Interaction	0.0230.0020.0080.5500.0700.2470.158		

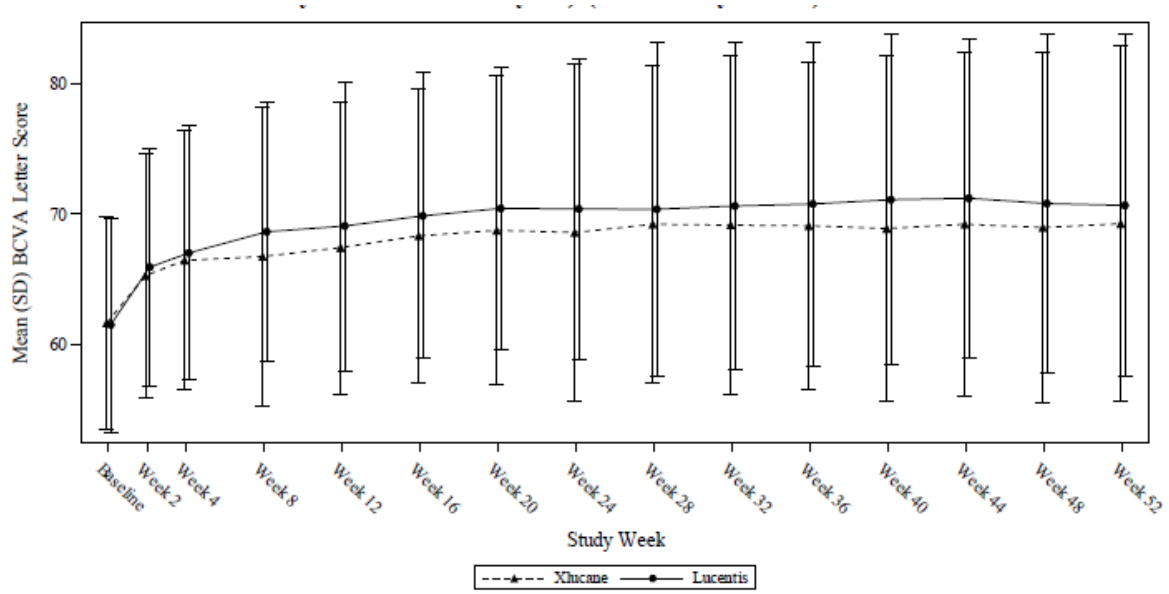
A sensitivity analysis using ANCOVA by week for change from Baseline in the BCVA letter score in the study eye (observed data for secondary estimand analyses) for the FAS produced similar results to the primary analysis. At Week 8, the LS means (SE) difference for Ximluci versus Lucentis was -1.94 (0.688) with 95% CI -3.29 to -0.59 letters for data missing completely at random (MCAR) and -1.65 (0.676) with 95% CI -2.97 to -0.33 letters for data missing not at random (MNAR).Likewise an ANCOVA by week for change from Baseline in the BCVA letter score in the study eye (observed data for secondary estimand analyses) for the FAS produced similar results to the primary analysis using BOCF and LOCF to impute for missing and non-evaluable data. At Week 8, the LS means (SE) difference for Ximluci versus Lucentis was -1.67 (0.657) with 95% CI -2.96 to -0.38 letters using BOCF and -1.41 (0.703) with 95% CI -2.79 to 0.03 using LOCF.

Secondary endpoints

Change in BCVA letters at Week 4, Week 12, Week 16, Week 24, Week 36, and Week 52 compared to Baseline using the ETDRS protocol for the study eye.

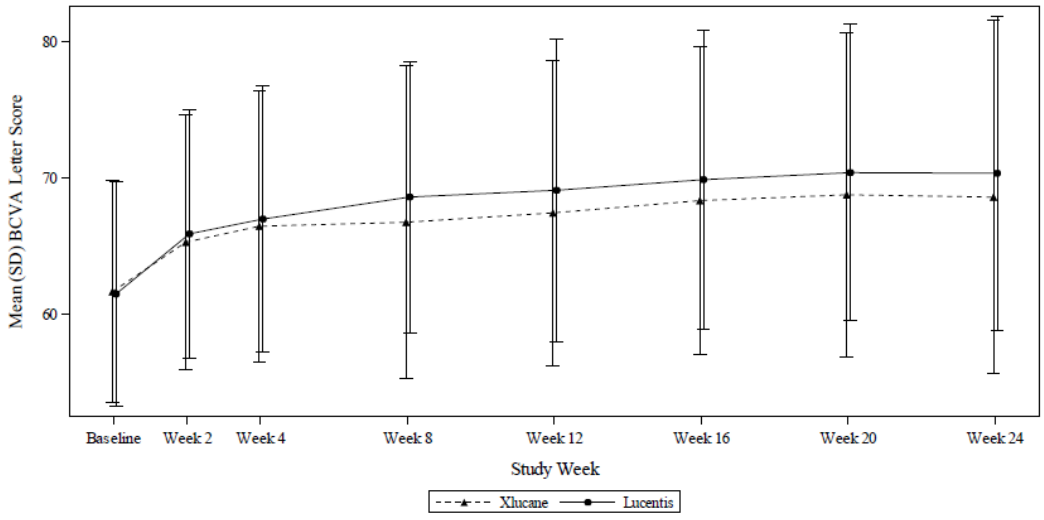
Descriptive statistics showing BCVA letter score by visit are shown in Table 11. This information is also presented graphically in Figure 3. Improvements in visual acuity were observed in both treatment groups at Weeks 4, 12, 16, 24, 36, and 52 with increases from Baseline in mean BCVA letter score observed at all visits. Small numerical differences in BCVA letter scores (by approximately 1 to 2.5 letters) were observed across the groups.

Figure 2: Mean (SD) Profile of the BCVA Letter Score in the Study Eye (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)



Abbreviations: BCVA, best corrected visual acuity; FAS, full analysis set; SD, standard deviation.
Note: Presented statistics are based on the FAS and the randomised treatment.
Source: Figure 14.2.1.1.1.1

Figure 3: Mean (SD) Profile of the BCVA Letter Score in the Study Eye (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)



Presented statistics are based on the FAS and the randomised treatment.

Table 11: Change from Baseline in the BCVA Letter Score in the Study Eye – Primary Analysis MMRM (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

Time point **Statistic**	**Model effects (p-**	**Ximluci** **N=292**	**Lucentis** **N=290**

	value)		
Week 4 LS Means (SE) 95% CI LS Means Diff (95% CI) P value		4.14 (0.451) 3.26 to 5.03	4.82 (0.457) 3.92 to 5.72 -0.68 (-1.78, 0.43) 0.229
Week 8 LS Means (SE) 95% CI LS Means Diff (95% CI) P value		**4.57 (0.527)** **3.54 to 5.61**	**6.37 (0.537)** 5.31 to 7.42 -1.79 (-3.14, -0.45) 0.009
Week 12 LS Means (SE) 95% CI LS Means Diff (95% CI)		5.15 (0.585) 4.0 to 6.29	6.54 (0.596) 5.37 to 7.71 -1.39 (-2.92, 0.13) 0.073
Week 16 LS Means (SE) 95% CI LS Means Diff (95% CI) P value		5.82 (0.595) 4.66 to 6.99	7.22 (0.606) 6.03 to 8.41 -1.40 (-2.95, 0.15) 0.077
Week 24 LS Means (SE) 95% CI LS Means Diff (95% CI) P value		5.82 (0.633) 4.58 to 7.06	8.09 (0.643) 6.83 to 9.35 -2.27 (-3.93 , -0.61) 0.007
Week 36 LS Means (SE) 95% CI LS Means Diff (95% CI) P value		6.14 (0.697) 4.78 to 7.51	8.43 (0.703) 7.05 to 9.81 -2.28 (-4.13, -0.43= 0.016
Week 52 LS Means (SE) 95% CI LS Means Diff (95% CI) P value		6.36 (0.802) 4.78 to 7.93	7.82 (0.810) 6.23 to 9.41 -1.46 (-3.62, 0.69) 0.183

Model effects (p-value)			
Treatment			
Baseline BCVA Letters	0.013		
Geographical Region	0.001		
Eye Colour	0.008		
Visit	0.297		
Treatment-by-Visit Interaction	0.011		
Baseline BCVA Letters-by-Visit Interaction	0.317		
	0.034		

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; FAS, full analysis set; IE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error. Notes: The objective of the primary estimand analysis was to estimate the treatment differences under the scenario of no IEs. Only evaluable data were included in this analysis. No data were imputed prior to analysis but the MMRM analysis employs a hypothetical strategy, assuming that non-evaluable and missing data due to IEs are missing at random. P-values for LS mean differences are 2-sided and test for non-zero difference between the treatments. Presented statistics are based on the FAS and the randomised treatment. Source: Table 14.2.1.1.2

Percentage of subjects with gain of ≥15 letters using ETDRS, evaluated as change at Week 4, Week 8, Week 24, and Week 52 compared to Baseline in the study eye

The percentage of subjects with a gain of ≥15 BCVA letters compared to Baseline increased over the time points in both the Ximluci and Lucentis groups. A slightly higher percentage of subjects in the Lucentis group had a gain of ≥15 letters compared to the Ximluci group across the time points. In the Ximluci group, 6.8% of subjects at Week 8, 12.0% at Week 16, 15.8% at Week 24, and 17.1% at Week 52 had a gain of ⩾15 letters compared to Baseline. In the Lucentis group, 14.1% of subjects at Week 8, 17.6% at Week 16, 18.6% at Week 24, and 21.4% at Week 52 had a gain of ⩾15 letters compared to Baseline. (Table 12).

Table 12: Percentage of Subjects With Gain of ≥15 BCVA Letters Compared to Baseline in the Study Eye – Descriptive Statistics (Evaluable Data for Estimand 1 Analyses) (Full Analysis Set)

Time point, Responder: Gain of ≥15 BCVA Letters Compared to Baseline in the Study Eye	**Ximluci** **N=292 (%)**	**Lucentis** **N=290 (%)**
Week 4 Responder	13 (4.5)	26 (9.0)
Missing	16 (5.5)	14 (4.8)
Week 8 Responder	20 (6.8)	41 (14.1)
Missing	28 (9.6)	36 (12.4)
Week 24 Responder	46 (15.8)	54 (18.6)
Missing	53 (18.2)	61 (21)
Week 52 Responder	50 (17.1)	62 (21.4)
Missing	80 (27.4)	86 (29.7)

Change from Baseline in the Percentage of Subjects With Loss of <15 BCVA Letters

The percentage of subjects who had a loss of <15 BCVA letters compared to Baseline decreased slightly over the 52 weeks of the study but still remained high in both the Ximluci and Lucentis groups, indicating subjects in both groups responded well to treatment. The results were similar between the Ximluci and Lucentis groups across all post-Baseline visits. At Week 24, the percentage of subjects who had a loss of <15 BCVA letters compared to Baseline was 78.8% in the Ximluci group and 77.9% in the Lucentis group. At Week 52, the percentage of subjects who had a loss of <15 BCVA letters compared to Baseline was 68.8% in the Ximluci group and 67.6% in the Lucentis group.

Table 13: Percentage of Subjects With Loss of <15 BCVA Letters Compared to Baseline in the Study Eye – Descriptive Statistics (Evaluable Data for Estimand 1 Analyses) (Full Analysis Set)

Time point, Responder: Loss of <15 BCVA Letters Compared to Baseline in the Study Eye	**Ximluci N=292 (%)**	**Lucentis N=290 (%)**
Week 2 Responder	270 (92.5)	269 (92.8)
Missing	22 (7.5)	20 (6.9)
Week 4 Responder	275 (94.2)	274 (94.5)
Missing	16 (5.5)	14 (4.8)
Week 8 Responder	262 (89.7)	253 (87.2)
Missing	28 (9.6)	36 (12.4)
Week 12 Responder	253 (86.6)	244 (83.8)
Missing	33 (11.3)	43 (14.8)
Week 16 Responder	236 (80.8)	230 (79.0)
Missing	50 (17.1)	56 (19.3)
Week 20 Responder	241 (82.5)	232 (80.0)
Missing	47 (16.1)	55 (19)
Week 24 Responder	230 (78.8)	226 (77.9)
Missing	53 (18.2)	61 (21)
Week 52 Responder	201 (68.8)	196 (67.6)
Missing	80 (27.4)	86 (29.7)

Change in central foveal thickness (CFT) in the study eye measured by OCT at Week 2, Week 4, Week 8, Week 16, Week 24, Week 36, and Week 52 compared to Baseline

At Baseline, the mean CFT in the study eye measured by OCT was 358.4 µm in the Ximluci group and 383.7 µm in the Lucentis group. A comparable decrease in CFT was observed between treatment groups at all time points over the 52 weeks of the study (Figure 4). When comparing change from

baseline in CFT with that of BCVA letter score between the treatment groups, the data does not show any directional consistency.

Table 14: Central Foveal Thickness in the Study Eye Measured by Optical Coherence Tomography – Descriptive Statistics (Evaluable Data for Estimand 1 Analyses) (Full Analysis Set)

Central Foveal Thickness (µm) **Time point** **Statistic**	**Ximluci** **N=292**	**Lucentis** **N=290**
Baseline (n)	292	290
Mean (SD)	358.4 (98.08)	383.7 (112.26)
Week 2 CFB	267	269
Mean (SD)	-80.5 (77.45)	-97.8 (90.69)
Week 4 CFB	272	273
Mean (SD)	-86.0 (87.04)	-104.0 (97.09)
Week 8 CFB	263	254
Mean (SD)	-97.6 (92.31)	-114.9 (100.91)
Week 12 CFB	255	247
Mean (SD)	-100.7 (92.49)	-117.1 (105.48)
Week 16 CFB	242	234
Mean (SD)	-102.5 (94.81)	-122.9 (105.18)
Week 20 CFB	243	235
Mean (SD)	-102.6 (97.10)	-124.3 (102.32)
Week 24 CFB	238	227
Mean (SD)	-102.3 (95.31)	-125.6 (103.88)
Week 36 CFB	222	234
Mean (SD)	-100.5 (101.24)	-129.4 (105.69)
Week 52 CFB	211	201
Mean (SD)	-105.3 (100.33)	-127.7 (108.63)

The mean (SD) profile of the CFT in the study eye (evaluable data for primary estimand analyses) for the FAS is displayed in Figure 4.

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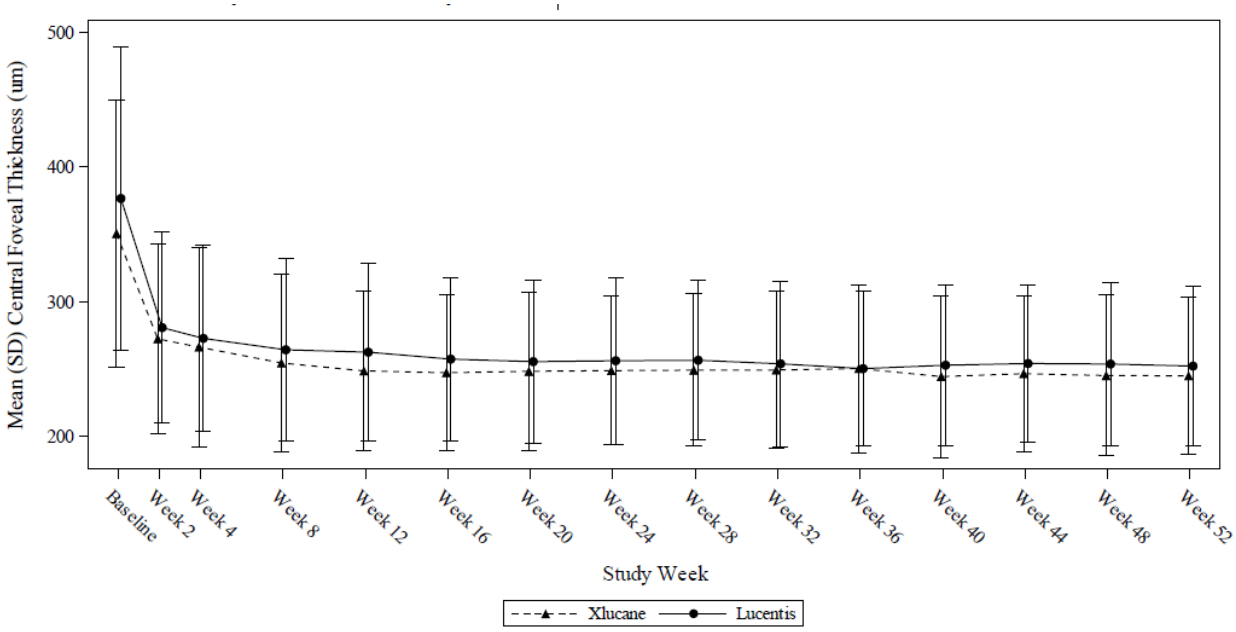
Figure 4: Mean (SD) Profile of the Central Foveal Thickness in the Study Eye Measured by Optical Coherence Tomography (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)



The MMRM analysis (evaluable data for Estimand 1 analyses) for the change from Baseline in CFT in the study eye for the FAS is presented in Table 15. The changes from Baseline in CFT in the study eye were similar between the Ximluci and Lucentis group over the first 52 weeks of the study and no statistically significant differences between treatment groups were observed at any time point. Similar results were seen with ANCOVA analyses using a missing completely at random assumption and also when a missing completely at random assumption was made. The analyses were repeated for Estimand 2 with broadly similar results.

Table 15: Change from Baseline in the CFT in the Study Eye Measured by Optical Coherence Tomography – MMRM (Evaluable Data for Estimand 1 Analyses) (Full Analysis Set)

Time point **Statistic**	**Ximluci** **N=292**	**Lucentis** **N=291**
MMRM for Change from Baseline in the CFT (um)		
Week 2 LS Means SE 95% CI LS means diff (95% CI)	-87.42 (3.761) -94.80 to -80.03	-88.66 (3.800) -96.12 to -81.201.24 (-7.94, 10.42)
Week 4 LS Means SE 95% CI LS means diff (95% CI)	-93.85 (4.040)-101.78 to -85.92	-95.51 (4.082)-103.53 to -87.501.67 (-8.4, 11.74)
Week 8 LS Means SE	-105.77 (4.020)-	-104.65 (4.084)-112.67 to -96.64-1.11

95% CI LS means diff (95% CI)	113.66 to -97.87	(-11.14, 8.92)
Week 12 LS Means SE 95% CI LS means diff (95% CI)	-112.03 (3.928)- 119.74 to -104.32-	-105.26 (3.994)- 113.11 to -97.42-6.77 (-16.49, 2.95)
Week 16 LS Means SE 95% CI LS means diff (95% CI)	-114.35 (3.767)- 121.75 to -106.96	-110.52 (3.832)- 118.04 to -102.99- 3.84 (-13.03, 5.36)
Week 20 LS Means SE 95% CI LS means diff (95% CI)	-115.06 (3.818) -122.55 to -107.56	-111.26 (3.883)- 118.89 to -103.63-3.8 (-13.15, 5.56)
Week 24 LS Means SE 95% CI LS means diff (95% CI)	-115.06 (3.807)- 122.53 to -107.58	-111.17 (3.873)- 118.77 to -103.56- 3.89 (-13.21, 5.43)
Week 36 LS Means SE 95% CI LS means diff (95% CI)	-114.19 (3.991) -122.03 to -106.36	-116.02 (4.031) -123.93 to -108.10 1.82 (-8.02, 11.66)
Week 52 LS Means SE 95% CI LS means diff (95% CI)	-117.44 (4.017) -125.33 to -109.55	-115.14 (4.075) -123.14 to -107.14 -2.30 (-12.26, 7.65)

Model effects (p-value): Treatment 0.605; Baseline CFT <0.0001; Geographical Region 0.833; Eye Colour 0.118; Visit <0.0001; Treatment-by-Visit Interaction 0. 2839; Baseline CFT by Visit Interaction <0.0001

Notes: The objective of the estimand 1 analysis was to estimate the treatment differences under the scenario of no IEs. Evaluable data were any data collected which were not impacted by an IE. Only evaluable data were included in this analysis. No data were imputed prior to analysis but the MMRM analysis employs a hypothetical strategy, assuming that non-evaluable and missing data due to IEs are missing at random. Presented statistics are based on the FAS and the randomised treatment. Source: Table 14.2.2.3.1.2

A sensitivity analysis using ANCOVA by week for change from Baseline in the CFT in the study eye (evaluable data for Estimand 1 analyses) for the FAS provided similar results.

Change in total size of choroidal neovascular leakage area in the study eye measured by FA at Week 24 and Week 52 compared to Baseline

A similar reduction in the total size of choroidal neovascular leakage area in the study eye was observed in both treatment groups. At Baseline, the mean total size of choroidal neovascular leakage area in the study eye measured by FA was 6.278 mm2 in the Ximluci group and 5.866 mm^2 in the Lucentis group. At Week 24, the mean change from Baseline in the total size of choroidal neovascular leakage area was -3.601 mm^2 in the Ximluci group and -3.320 mm^2 in the Lucentis group. At Week 52, the mean change from Baseline in the total size of choroidal neovascular leakage area was -4.130 mm^2 in the Ximluci group and -3.494 mm^2 in the Lucentis group.

Change in total size of CNV in the study eye measured by FA at Week 24 and Week 52 compared to Baseline

Similar decrease in total size of CNV in the study eye was observed in both treatment groups. At Baseline, the mean total size of CNV in the study eye measured by FA was 5.509 mm^2 in the Ximluci group and 5.213 mm^2 in the Lucentis group. At Week 24, the mean change from Baseline in the total size of CNV was -0.789 mm^2 in the Ximluci group and -0.503 mm^2 in the Lucentis group. At Week 52, the mean change from Baseline in the total size of CNV was -1.465 mm2 in the Ximluci group and -0.798 mm2 in the Lucentis group.

Change from Baseline in Size and/or Number of Intraretinal Cystoid Space (Cysts), Subretinal Fluid, and Retinal Pigment Epithelium Detachments in the Study Eye

Intraretinal cysts (assessed by qualitative morphology based OCT)

At Baseline, in the Ximluci group, 131 subjects (44.9%) had 0 cysts, 14 subjects (4.8%) had 0-1 cysts, 19 subjects (6.5%) had 1-2 to 5 cysts, 126 subjects (43.2%) had 2 to >5 cysts, and 2 subjects 0.7%) had missing data.

At Baseline, in the Lucentis group, 140 subjects (48.3%) had 0 cysts, 9 subjects (3.1%) had 0-1 cysts, 16 subjects (5.5%) had 1-2 to 5 cysts, 123 subjects (42.4%) had 2 to >5 cysts, and 2 subjects (0.7%) had missing data.

At the last on-treatment assessment, in the Ximluci group, 207 subjects (70.9%) had 0 cysts, 10 subjects (3.4%) had 0-1 cysts, 27 subjects (9.2%) had 1-2 to 5 cysts, 43 subjects (14.7%) had 2 to >5 cysts, and 5 subjects (1.7%) had missing data. At the last on-treatment assessment, in the Lucentis group, 197 subjects (67.9%) had 0 cysts, 10 subjects (3.4%) had 0-1 cysts, 24 subjects (8.3%) had 1-2 to 5 cysts, 54 subjects (18.6%) had 2 to >5 cysts, and 5 subjects (1.7%) had missing data.

CMH analysis (evaluable data for Estimand 1 analyses) for intraretinal cystoid space (cysts) in the study eye measured by qualitative morphology-based OCT showed that at Week 24 and 52, there were no statistically significant differences between treatment groups in the cumulative proportion of subjects who had intraretinal cysts in any of the following categories: no more than 0 cysts, no more than 0-1 cysts, and no more than 1-2 to 5 cysts. At Week 52, for data MAR and when missing and non-evaluable data were imputed using BOCF, there were no significant differences between treatment groups in the cumulative proportion of subjects who had intraretinal cysts in any of the mentioned categories.

At Week 24, the difference (Ximluci versus Lucentis) in the cumulative proportion of subjects who had no more than 0 intraretinal cysts was 4.3% (90% CI: -2.0 to 10.5; 95% CI: -3.2 to 11.7) for data MAR. At Week 52, the difference (Ximluci versus Lucentis) in the cumulative proportion of subjects who had no more than 0 intraretinal cysts was 5.5% (90% CI: -1.0 to 11.9; 95% CI: -2.2 to 13.2) for data MAR.

Subretinal fluid

At Baseline, the mean subretinal fluid in the study eye was lower in the Ximluci group (34.3 µm) compared to the Lucentis group (50.1 µm). Decreases in subretinal fluid were observed at all post-Baseline visits in both treatment groups, with larger decreases from Baseline observed in the Lucentis group consistently across all time points. At the last on-treatment assessment, the mean subretinal fluid in the study eye was 8.2 µm in the Ximluci group and 15.5 µm in the Lucentis group.

The MMRM analysis (evaluable data for Estimand 1 analyses) for the change from Baseline in the amount of subretinal fluid in the study eye measured by OCT for the FAS at Week 24, showed the LS

means (SE) change from Baseline in subretinal fluid was -32.67 (2.209)µm in the Ximluci group and -32.29 (2.263)µm in the Lucentis group. The LS means (SE) difference for Ximluci versus Lucentis was -0.38 (2.838)µm (90% CI: -5.05 to 4.30; 95% CI: -5.95 to 5.20). At Week 52, the LS means (SE) change from Baseline in subretinal fluid was -34.88 (2.133) µm in the Ximluci group and -32.93 (2.180) µm in the Lucentis group. The LS means (SE) difference for Ximluci versus Lucentis was -1.95 (2.687) µm (90% CI: -6.38 to 2.48; 95% CI: -7.23 to 3.33).

Retinal pigment detachments

At Baseline, the mean width of retinal pigment epithelium detachments in the study eye was 3216.8 µm in the Ximluci group and 3114.9 µm in the Lucentis group. The mean height of retinal pigment epithelium detachments in the study eye was 224.8 µm in the Ximluci group and 213.3 µm in the Lucentis group.

Decreases in the width and height of retinal pigment epithelium detachments were observed at all post-Baseline visits in both treatment groups.

At the last on-treatment assessment, the mean change from Baseline in the width of retinal pigment epithelium detachments was -204.2 µm in the Ximluci group and -173.9 µm in the Lucentis group.

At the last on-treatment assessment, the mean change from Baseline in the height of retinal pigment epithelium detachments was -81.7 µm in the Ximluci group and -66.1 µm in the Lucentis group.

Ancillary analyses

Subgroup analyses

The change from Baseline in the BCVA letter score in the study eye was presented and analysed by the following subgroups, which were related to the stratification factors used for randomisation:

- Eye colour (light iris or dark iris)
- BCVA letters at Baseline (≤ 55 letters, 56 - 65 letters, ≥ 66 letters)
- Geographical region where enrolled (Asia, Europe, or America)

Table 16: Change From Baseline in the BCVA Letter Score in the Study Eye – MMRM Analysis by Eye Colour (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

		Dark Iris		**Light Iris**	
Time point **Statistic**		**Ximluci** **N=140**	**Lucentis** **N=139**	**Ximluci** **N=152**	**Lucentis** **N=151**
Week 4 LS Means (SE) LS Means Diff (95% CI) P-value		4.13 (0.611)	4.69 (0.609) -0.56 (-2.17, 1.05) 0.494	4.18 (0.608)	4.96 (0.619) -0.78 (-2.30,0.74) 0.312
Week 8 LS Means (SE) LS Means Diff (95% CI)		5.00(0.73)	6.23 (0.74) -1.23 (-3.2, 0.73)	4.3 (0.72)	6.50 (0.725) -2.28 (-4.12, -0.44)

P-value			0.218		0.015
Week 12 LS Means (SE) LS Means Diff (95% CI) P-value		5.27 (0.834)	6.95 (0.830) -1.68 (-3.90, 0.55) 0.139	5.1 (0.80)	6.21 (0.809) -1.2 (-3.25, 0.93) 0.277
Week 16 LS Means (SE) LS Means Diff (95% CI) P-value		5.92 (0.834)	7.58 (0.844) -1.66 (-3.93, 0.60) 0.150	5.76 (0.811)	6.94 (0.822) -1.18 (-3. 31, 0.95) 0.279
			220.40		
Week 24 LS Means (SE) LS Means Diff (95% CI) P value		5.96 (0.893)	8.06 (0.903) -2.11 (-4.54, 0.33) 0.090	5.72 (0.859)	8.15 (0.870) -2.43 (-4.71, -0.16) 0.036
Week 36 LS Means (SE) LS Means Diff (95% CI) P value		6.39 (0.989)	8.00 (0.992) -1.61 (-4.31, 1.08) 0.240	5.95 (0.951)	8.82 (0.956) -2.88 (-5.41 , -0.34) 0.026
Week 52 LS Means (SE) LS Means Diff (95% CI) P value		6.53 (1.156)	8.59 (1.163) -2.06 (-5.23, 1.12) 0.203	6.22 (1.091)	7.25 (1.099) -1.04 (-3.98, 1.91) 0.490
Model effects (p-value) Treatment Baseline BCVA Letters Geographical Region Eye Colour Visit Treatment-by-Visit Interaction Baseline BCVA Letters by Visit Interaction Eye Colour by Visit Interaction	 0.013 0.001 0.008 0.982 0.013 0.392 0.039 0.152				

Eye Colour by Treatment Interaction Eye Colour by Treatment by Visit Interaction	0.854 0.441				

BCVA = Best Corrected Visual Acuity, CI = Confidence Interval, FAS = Full Analysis Set, IE = Intercurrent Event, LS = Least Squares, MMRM = Mixed Model with Repeated Measures, SE = Standard Error **Notes:** The objective of the primary estimand analysis was to estimate the treatment differences under the scenario of no IEs. Evaluable data is any data collected which was not impacted by an IE. Only evaluable data are included in this analysis. No data are imputed prior to analysis but the MMRM analysis employs a hypothetical strategy, assuming that non-evaluable and missing data due to IEs are missing at random. P-values for LS mean differences are 2-sided and test for non-zero difference between the treatments. Presented statistics are based on the FAS and the randomised treatment.

Table 17: Change From Baseline in the BCVA Letter Score in the Study Eye – MMRM Analysis by BCVA Letters at Baseline Group (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

	≤ 55 letters		56 – 65 letters		≥ 66 letters	
Time point **Statistic**	**Ximluci** **N=77**	**Lucentis** **N=77**	**Ximluci** **N=105**	**Lucentis** **N=100**	**Ximluci** **N=110**	**Lucentis** **N=113**
Week 4 LS Means (SE) LS Means Diff (95% CI) P-value	4.03 (0.804)	6.30 (0.800)-2.27(-4.45, -0.09 0.041	4.69 (0.690)	5.46 (0.701) -0.77 (-2.61, 1.08(-2.6, 1.1) 0.413	3.87 (0.699)	3.47 (0.704) 0.4 (-1.40, 2.19) 0.664
Week 8 LS Means (SE) LS Means Diff (95% CI) P-value	4.68 (0.966)	7.46 (0.967) -2.78 (-5.42, -0.13) 0.040	5.53 (0.818)	7.54 (0.847) -2.01 (-4.25, 0.23) 0.079	3.74 (0.834)	4.78 (0.837) -1.04 (-3.23, 1.16) 0.354
Week 12 LS Means (SE) LS Means Diff (95% CI) P-value	5.66 (1.095)	7.66 (1.089) -1.99 (-4.99, 1.01) 0.192	6.25 (0.923)	7.40 (0.959) -1.15 -3.70, 1.40) 0.376	3.89 (0.932)	5.24 (0.937) -1.35 (-3.84, 1.14) 0.287
Week 16 LS	6.82	8.85	6.25	8.26	4.91	5.42 (0.954)

Means (SE) LS Means Diff (95% CI) P-value	(1.119)	(1.110) -2.04 (-5.10, 1.03) 0.192	(0.946)	(0.979) -2.02 -4.63, 0.59) 0.129	(0.946)	-0.51 -3.05, 2.02) 0.690
Week 24 LS Means (SE) LS Means Diff (95% CI) P value	6.03 (1.194)	8.62 (1.181) -2.6 (-5.86, 0.67) 0.119	6.71 (1.013)	9.04 (1.040) -2.33 (-5.12, 0.46) 0.101	5.02 (0.997)	7.09 (1.012) -2.08 (-4.76, 0.61) 0.130
Week 36 LS Means (SE) LS Means Diff (95% CI) P value	7.21 (1.340)	9.65 (1.310) -2.44 (-6.10, 1.21) 0.190	6.25 (1.125)	9.63 (1.144) -3.38 (-6.48, -0.28) 0.033	5.46 (1.106)	6.76 (1.118) -1.31 (-4.30, 1.69) 0.392
Week 52 LS Means (SE) LS Means Diff (95% CI) P value	6.77 (1.571)	9.98 (1.538) -3.21 (-7.51, 1.08) 0.142	7.10 (1.301)	9.09 (1.327) -1.99 (-5.60, 1.62) 0.279	5.43 (1.277)	5.48 (1.294) -0.05 (-3.55, 3.44) 0.977
Model effects (p-value): Treatment0.010; Baseline BCVA Letters Group 0.040; Geographical Region 0.011; Eye Colour 0.355; Visit <0.0001; Treatment by Visit Interaction 0.324; Baseline BCVA Letters Group by Visit Interaction 0.557; Baseline BCVA Letters Group by Treatment Interaction 0.774; Baseline BCVA Letters Group by Treatment-by- Visit Interaction 0.005						

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; FAS, full analysis set; IE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error. Notes:The objective of the primary estimand analysis was to estimate the treatment differences under the scenario of no IEs. Evaluable data is any data collected which was not impacted by an IE. Only evaluable data are included in this analysis. No data are imputed prior to analysis but the MMRM analysis employs a hypothetical strategy, assuming that non-evaluable and missing data due to IEs are missing at random. P-values for LS mean differences

are two-sided and test for non-zero difference between the treatments. Presented statistics are based on the FAS and the randomised treatment.

Table 18: Change From Baseline in the BCVA Letter Score in the Study Eye – MMRM Analysis by Geographical Region (Evaluable Data for Primary Estimand Analyses) (Full Analysis Set)

	Asia		**Europe**		**America**	
Time point **Statistic**	**Ximluci** **N=43**	**Lucentis** **N=40**	**Ximluci** **N=212**	**Lucentis** **N=212**	**Ximluci** **N=37**	**Lucentis** **N=38**
Week 4 LS Means (SE) LS Means Diff (95% CI) P-value	2.54 (1.068)	5.03 (1.154) -2.49 (-5.5, 0.52) 0.105	5.21 (0.468)	5.33 (0.463) -0.12 (-1.40, 1.16) 0.857	3.79 (1.120)	5.87 (1.117) -2.08(-5.16, 1.00) 0.186
Week 8 LS Means (SE) LS Means Diff (95% CI) P-value	3.20 (1.299)	6.24 (1.463) -3.04 (-6.82, 0.73) 0.114	5.62 (0.565)	6.80 (0.563) -1.19 (-2.74, 0.39) 0.135	4.07 (1.378)	8.15 (1.365) -4.08 (-7.85, -0.31) 0.034
Week 12 LS Means (SE) LS Means Diff (95% CI) P-value	4.07 (1.480)	7.83 (1.667) -3.75 (-8.07, 0.56) 0.088	6.19 (0.637)	6.82 (0.636)-0.63 (-2.39, 1.13) 0.480	4.42 (1.554)	8.20 (1.554) -3.78 (-8.06, 0.50) 0.083
Week 16 LS Means (SE) LS Means Diff (95% CI) P-value	5.32 (1.530)	7.75 (1.709) -2.43 (-6.87, 2.01) 0.283	6.77 (0.649)	7.57 (0.647) -0.8 (-2.59, 0.99) 0.381	5.11 (1.591)	9.07 (1.585) -3.96 (-8.34, 0.43) 0.077
Week 24 LS Means (SE) LS Means Diff (95%	5.23 (1.722)	8.71 (1.895) -3.48 (-8.46, 1.49) 0.169	7.11 (0.688)	8.60 (0.688) -1.49 (-3.40, 0.41) 0.124	2.91 (1.687)	8.97 (1.657) -6.07 (-10.69, -1.45) 0.010

CI) P value						
Week 36 LS Means (SE) LS Means Diff (95% CI) P value	5.57 (1.955)	7.78 (2.157) -2.21 (-7.88, 3.45) 0.443	7.28 (0.769)	8.84 (0.762) -1.56 (-3.68, 0.56) 0.149	4.46 (1.877)	10.60 (1.839) -6.15 (-11.28, -1.01) 0.019
Week 52 LS Means (SE) LS Means Diff (95% CI) P value	6.03 (2.445)	7.80 (2.665) -1.77 (-8.83, 5.28) 0.621	7.57 (0.892)	8.33 (0.888) -0.76 (-3.23, 1.70) 0.544	4.11 (2.176)	8.73 (2.149) -4.62 (-10.60, 1.36) 0.129
Model effects (p-value): Treatment 0.005; Baseline BCVA Letters 0.002; Geographical Region 0.515; Eye Colour 0.288; Visit 0.015; Treatment by Visit Interaction 0.269; Baseline BCVA Letters by Visit Interaction 0.111; Geographical Region by Visit Interaction 0.080; Geographical Region by Treatment Interaction 0.205; Geographical Region by Treatment-by-Visit Interaction 0.825						

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; FAS, full analysis set; IE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error.
Notes: The objective of the primary estimand analysis was to estimate the treatment differences under the scenario of no IEs. Evaluable data is any data collected which was not impacted by an IE. Only evaluable data are included in this analysis. No data are imputed prior to analysis but the MMRM analysis employs a hypothetical strategy, assuming that non-evaluable and missing data due to IEs are missing at random. Presented statistics are based on the FAS and the randomised treatment.

Summary of main efficacy results

The following table summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 19: Summary of Efficacy for trial Xplore

Title: Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Ximluci versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration (XBR1001)				
Study identifier	XBR1001 EudraCT Number: 2018-002930-19			
Design	A phase 3 multicentre, double-blind (double-masked), randomised, parallel group study in subjects with wet age-related macular degeneration. 583 subjects were enrolled and randomised in a 1:1 ratio to receive either Lucentis (0.05 mL of 10 mg/mL ranibizumab) or the investigational product, Ximluci (0.05 mL of 10 mg/mL ranibizumab), in the study eye once every 4 weeks/monthly for 52 weeks (ie, 12 months). As agreed with EMA, an unmasked analysis of efficacy and safety endpoints as well as PK and immunogenicity was performed when 6-month (ie, 24 weeks) data for all subjects on the study was collected. The MAA is based on a data cut off point of all patients who completed 6 months of treatment. The remaining data will be provided to EMA during the review phase in the Day 120 response package.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks not applicable not applicable	
Hypothesis	Equivalence			
Treatments groups	Ximluci (biosimilar candidate)		N = 292 randomised to receive Ximluci 0.5mg IVT in the study eye 4 weekly for 12 months (13 doses)	
	Lucentis (reference product)		N = 290 randomised to receive Lucentis 0.5mg IVT in the study eye 4 weekly for 12 months (13 doses)	
Endpoints and definitions	Primary endpoint	BCVA Week 8	Change in BCVA at Week 8 from Baseline using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol for the study eye. To prove the 2 products to be biosimilar, the confidence limits for the LS means difference had to be within the equivalence margin of +/- 3.5 letters (95% CI).	
	Secondary endpoint	BCVA other	Change in BCVA from baseline at Week 4, Week 12, Week 16, Week 24, *(Week 36 and Week 52)* using the ETDRS protocol for the study eye.	
Database lock	Date of Interim Analysis Data Snapshot: 10 June 2021			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set Week 8			
Descriptive statistics and estimate variability	Treatment group	Ximluci	Lucentis	
	Number of subject	292	290	
	Primary endpoint Mean change from baseline in BCVA (letters) Week 8 (Primary estimand)	4.57	6.37	
	95% CI	3.54 to 5.61	5.31 to 7.42	
	Secondary endpoint BCVA week 4	4.14	4.82	
	95%CI	3.26 to 5.03	3.92 to 5.72	
		Ximluci N = 292	Lucentis N = 290	

Title: Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Ximluci versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration (XBR1001)				
Study identifier	XBR1001 EudraCT Number: 2018-002930-19			
	Secondary endpoint BCVA week 12 (95% CI)	5.15 4.0 to 6.29	6.54 5.37 to 7.71	
	Secondary endpoint BCVA week 16 (95% CI)	5.82 4.66 to 6.99	7.22 6.03 to 8.41	
	Secondary endpoint BCVA week 24 (95% CI)	5.82 4.58 to 7.06	8.09 6.83 to 9.35	
	Secondary endpoint BCVA week 36 (95% CI)	6.14 4.78 to 7.51	8.43 7.05 to 9.81	
	Secondary endpoint BCVA week 52 (95% CI)	6.36 4.78 to 7.93	7.82 6.23 to 9.41	

Effect estimate per comparison	Primary endpoint Mean change from baseline BCVA at Week 8 MMRM MAR)	Comparison groups	Ximluci v Lucentis
		LS mean difference between Ximluci and Lucentis week 8	-1.79
		95% CI	-3.14 to -0.45
		P-value	0.009
	Secondary endpoint Mean change from baseline BCVA at Week 4 MMRM MAR)	Comparison groups	Ximluci v Lucentis
		LS mean difference between Ximluci and Lucentis Week 4	-0.68
		95% CI	-1.78 to 0.43
		P-value	0.229
	Secondary endpoint: Mean change from baseline BCVA at Week 12 MMRM MAR)	Comparison groups	Ximluci v Lucentis
		LS mean difference between Ximluci and Lucentis Week 12	-1.39
		95% CI	-2.92 to 0.13
		P-value	0.073
	Secondary endpoint: Mean change from baseline BCVA at Week 16 MMRM MAR)	Comparison groups	Ximluci v Lucentis
		LS mean difference between Ximluci and Lucentis Week 16	-1.40
		95% CI	-2.95 to 0.15
		P-value	0.077
		Comparison groups	Ximluci v Lucentis

Title: Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Ximluci versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration (XBR1001)			
Study identifier	XBR1001 EudraCT Number: 2018-002930-19		
	Secondary endpoint: Mean change from baseline BCVA at Week 24 MMRM MAR)	LS mean difference between Ximluci and Lucentis Week 20	-2.23
		95% CI	-3.93 to -0.61
		P-value	0.007
	Secondary endpoint: Mean change from baseline BCVA at Week 36 MMRM MAR)	LS mean difference between Ximluci and Lucentis Week 20	-2.28
		95% CI	-4.13 to -0.43
		P-value	0.016
	Secondary endpoint: Mean change from baseline BCVA at Week 52 MMRM MAR)	LS mean difference between Ximluci and Lucentis Week 20	-1.46
		95% CI	-3.62 to 0.69
		P-value	0.183

2.4.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant submitted one randomised double blind active controlled equivalence study (Xplore) with Lucentis the reference product for intravitreal ranibizumab as the active control. Patients were treated with monthly intravitreal injections of Ximluci or Lucentis over a 12-month study period. Although in Europe the most frequent regimen for the treatment with ranibizumab is Treat and Extend, the monthly dosages represent a suitable treatment regimen for a clinical study comparing Ximluci and Lucentis. The selected monthly regimen provides the maximum ranibizumab available dose, which is a conservative approach from a methodological point of view. Since this was the regimen tested versus sham in the original dossier of Lucentis for the treatment of nAMD, it can be considered an adequate reference.

The study was conducted in patients aged over 50 with neovascular age-related macular degeneration. The study has a duration of 52 weeks. At the time of submission of the application for marketing authorisation data on efficacy was only available up to Week 24. Further data up to and including 52 weeks was submitted in the course of the procedure.

Given that this is a biosimilar application and the aim is to demonstrate similarity to the reference product the submission of one study is acceptable. It is also acceptable to allow the extrapolation of findings from the pivotal study in one indication to the other indications of the authorised reference product in light of the Applicant's justification.

The Applicant obtained a number of scientific advice letters from the CHMP, which mainly focused on the inclusion/exclusion criteria, the primary endpoint and the equivalence margin. In general, the Applicant has followed the advice.

The inclusion and exclusion criteria are generally suitable for a clinical efficacy study evaluating equivalence for biosimilarity. The population included patients aged 50 or more with a new diagnosis of nAMD, a baseline visual acuity between 49 and 73 letters inclusive and a total lesion area ≤ 9-disc areas. The Applicant has followed scientific advice to recruit a reasonably homogeneous population in order to increase the chances that any differences between products can be detected. However, regarding the exclusion criteria for myopia (Spherical equivalent of the refractive error in the study eye that demonstrated more than 8 diopters of myopia), the applicant has not followed the

recommendation of the Scientific Advice EMA/CHMP/SAWP/778937/2018 that stated that patients with 6 or more diopters of myopia should not be included. However, this was accepted as this criterion was aligned with one of the registration trials for ranibizumab (MARINA/ANCHOR) and the risk of harm to patients was considered low.

The Applicant, in the course of the product development, changed the primary endpoint from change from baseline in central foveal thickness at Week 8 to change from baseline in best corrected visual acuity at Week 8. The choice of this endpoint had been encouraged during scientific advice~~, although the Applicant's initial proposal of 'change in the central foveal thickness' (CFT) as the primary endpoint was considered acceptable by the CHMP in the previous advice as CFT is an objective measurement. It was also noted by the CHMP that VA measurements register the patient's performance, which may be affected by factors other than eye functionality, such as cognitive health and interaction with study personnel. Using an endpoint with low variability allows for fewer patients to undergo study procedures and medication CFT, the variable for the proposed primary endpoint, is intrinsically related to the pathology of the indication, wet AMD, and to the mode of action of ranibizumab~~.

Given, that it has been noted that in clinical trials the effect of Lucentis reaches a plateau at about 12 weeks, the use of change from baseline at 8 weeks was accepted as per scientific advice to be the most sensitive time point to detect any differences between Lucentis and Ximluci.

The Applicant also complied with advice to include a comparison of change in BCVA from baseline at other time points including week 4 as well as later time points. The Applicant also included CFT measured by OCT at a number of time points as secondary endpoint and has followed the recommendation of the Scientific Advice EMA/CHMP/SAWP/295631/2018 regarding the inclusion of one earlier time-point (1-2 weeks) for the assessment and to further strengthen the evidence for biosimilarity. In fact, the CST was the primary endpoint in the pivotal study of another biosimilar product of Lucentis currently authorized by EMA (Byooviz).

The remaining secondary endpoints e.g. a responder analysis for gain in ≥ 15 letters from baseline and loss of < 15 letters from baseline, change from baseline at different time points in central foveal thickness, changes in lesion size, volume of intra and subretinal fluid etc are all considered to be relevant.

Initially there were some uncertainties regarding the masking of the study. These have now been resolved and it is considered that there was appropriate masking of the study.

An interim analysis at Week 8 of change from baseline in BCVA (primary endpoint) was conducted once all recruited patients had either discontinued or completed 24 weeks of treatment. The Applicant has confirmed that there were robust systems in place to prevent unmasking following the interim analysis.

Biosimilarity was to be concluded if the 95% confidence intervals for the difference in mean change in BCVA at Week 8 between Ximluci and Lucentis was confined within the equivalence margin of ±3.5 letters. A meta-analysis of the ANCHOR and MARINA studies in Lucentis focusing on Week 8 data concluded that the difference in mean change in BCVA between treatment and placebo was 7.7 letters. In order to ensure that the proposed equivalence margin would preserve at least 50% of the lower limit of the 95% CI for the difference in mean change in BCVA between treatment arms an equivalence margin of ±3.5 letters was chosen. The choice of equivalence margin was supported by the EMA in recent scientific advice.

The study was conducted during the COVID 19 pandemic. As a consequence of protocol deviations related to the pandemic the Applicant changed their approach to the analysis of the primary endpoint in the protocol with a switch from a planned ANCOVA analysis to an estimand approach using a mixed model for repeated measures (MMRM) with missing data assumed to be missing at random.

The proportion of subjects (about 45%) having major protocol deviations up to and including Week 52, though high, was similar in both treatment arms. The most common major PDs in both groups were related to missed visits: "COVID-19 – missed visit" (16.1% of subjects in the Ximluci arm and 15.9% of subjects in the Lucentis arm).

Sixteen subjects (5.5%) in the Ximluci arm and 6 subjects (2.1%) in the Lucentis arm were mis-stratified. These were categorised as major protocol deviations. All stratification errors were related to baseline BCVA category where the site inadvertently entered the incorrect Baseline BCVA stratification group at the Randomisation visit.

An additional 4 subjects (2 subjects in the Ximluci group and 1 subject in the Lucentis group) had similar stratification errors related to the site entering the incorrect Baseline BCVA stratification group, but these were not recorded as major PDs under the category of "stratification error."

Whilst the applicant claims that the mis-stratification did not affect the overall balance of the assignment to the treatment arms, nevertheless the Applicant was asked to provide information on whether the mis-assignment had any impact on the sub-group analysis of the primary endpoint by baseline BCVA category. The Applicant has confirmed that actual BCVA was used in the sub-group analysis and therefore there was no impact on the sub-group analysis.

Efficacy data and additional analyses

The study met its primary endpoint. At week 8 the gain from baseline in BCVA for Ximluci was 4.6 letters (95% CI from 3.5 to 5.6 letters). For Lucentis the gain was 6.4 letters (95% CI from 5.3 to 7.4 letters). It should be noted that the gain in BCVA was numerically greater for Lucentis than Ximluci at all assessed time points both in the primary analysis and in sub-group analyses by iris colour and category of BCVA. The LS mean difference in change from baseline BCVA between the two treatment arms at Week 8 was – 1.8 letters with 95% CI from -3.1 to -0.4 letters. As the 95% CI were within the margins of ± 3.5 letters it can be concluded that equivalence has been demonstrated at Week 8, even though it could be concluded that Ximluci was statistically inferior to Lucentis at Week 8. Similar results to the primary analysis were also demonstrated in a number of sensitivity analyses. However, peak improvement in BCVA was seen at Week 20 rather than Week 12. Nevertheless, the proportional major changes from baseline were seen at weeks 4-8.

Small numerical differences in change from Baseline in BCVA letter score were observed between treatment groups at some visits, although there was some variability, the observed differences were relatively stable over 52 weeks. The convergence between the two treatment arms at Week 52 suggest that these differences did not increase over time. Given the lack of directional consistency of the observed numerical difference with the anatomical endpoints, this was concluded not to be due to any structural differences between the products.

Even though Ximluci and Lucentis were judged to be highly similar at the quality level and despite the fact that Ximluci met its primary endpoint at Week 8, a time-point that was thought to be most sensitive to differences in efficacy between the treatment arms, an increase in the difference in change in BCVA from baseline between the two treatment arms is seen at Week 20 and particularly at Week 24. At Week 20 the LS mean for change from baseline in BCVA was 6.1 for Ximluci and 8.1 for Lucentis. The LS mean difference was -1.9 with 95% CI from -3.5 to -0.3. At Week 24 the LS mean for change from baseline in BCVA was 5.8 for Ximluci and 8.1 for Lucentis. The LS mean difference was -2.3 with 95% CI -4.0 to -0.6.

The Applicant provided data for the second six months (weeks 28 to 52 in 4 weekly intervals) of treatment which showed that Lucentis continued to perform better than Ximluci and the lower 95% CI

for LS mean difference was below -3.5 letters for all time points in the second 6 months and below – 4 for all except week 28 and 52. However, the divergence between the two treatment arms at Week 52 was lower than at Week 24, suggesting that these differences did not increase over time.

High degree of similarity between the treatment arms was seen for a number of secondary endpoints. Ximluci and Lucentis demonstrate a high degree of similarity of treatment effects on sensitive anatomical endpoints including CFT, total size of CNV leakage area, number of intraretinal cysts, amount of sub-retinal fluid and size of retinal PEDs.

In the course of the procedure the Applicant has provided an acceptable justification for extrapolation of the indication to the remaining Lucentis indications.

2.4.7. Conclusions on the clinical efficacy

Based on the totality of the evidence, i.e. analytical biosimilarity, the fact that the pivotal trial demonstrated equivalence of Ximluci to Lucentis in change from baseline BCVA at week 8 (which was considered a sensitive timepoint) and similar improvements in anatomical endpoints, the CHMP concluded that biosimilarity of Ximluci to Lucentis has been demonstrated.

2.4.8. Clinical safety

The safety data reported includes 582 randomised subjects, of which 581 subjects were included in the SS.

All 292 subjects in the Ximluci group, and 289 out of 290 subjects in the Lucentis group were included in the safety set (SS); 1 subject in the Lucentis group was excluded from the SS because the subject withdrew consent and was not dosed with study drug.

Table 20: Subject Enrollment, Randomisation, and Dosing (Enrolled Set)

Subject Disposition	Overall N=1043 n (%)
Screened	1043
Rescreened	8 (0.8)
Screen Failure[a]	461 (44.2)
Subject did not fulfil all eligibility criteria	405 (38.8)
Subject withdraw consent	34 (3.3)
Principal investigator decision	0
Sponsor decision	3 (0.3)
Other	19 (1.8)
Randomised	582 (55.8)
Dosed	581 (55.7)

Subjects were randomised across 15 countries including the United States and countries in Europe, the Middle East, and Asia-Pacific. All 292 subjects randomised to the Ximluci group were dosed with study drug.

The majority of subjects were recruited from Europe (72.9%), followed by Asia (14.2%), and the United States (12.9%).

The mean overall ranibizumab exposure was 5.78 mg in the Ximluci group and 5.80 mg in the Lucentis group. The mean ranibizumab treatment duration was 311.9 days in the Ximluci group and 312.3 days in the Lucentis group.

A total of 184 subjects (63.0%) in the Ximluci group and 178 subjects (61.6%) in the Lucentis group received all 13 doses of ranibizumab over the study.

The extent of exposure for the Safety Set (SS) was similar between treatment groups is summarised in Table 21.

Table 21: Extent of Exposure (Safety Set)

Variable Statistic/Response	Xlucane N=292	Lucentis N=289	Overall N=581
Total Ranibizumab Doses, n(%)			
1	3 (1.0)	5 (1.7)	8 (1.4)
2	5 (1.7)	4 (1.4)	9 (1.5)
3	5 (1.7)	4 (1.4)	9 (1.5)
4	4 (1.4)	3 (1.0)	7 (1.2)
5	4 (1.4)	5 (1.7)	9 (1.5)
6	4 (1.4)	3 (1.0)	7 (1.2)
7	7 (2.4)	5 (1.7)	12 (2.1)
8	7 (2.4)	5 (1.7)	12 (2.1)
9	4 (1.4)	3 (1.0)	7 (1.2)
10	7 (2.4)	10 (3.5)	17 (2.9)
11	12 (4.1)	14 (4.8)	26 (4.5)
12	46 (15.8)	50 (17.3)	96 (16.5)
13	184 (63.0)	178 (61.6)	362 (62.3)
Overall Ranibizumab Exposure (mg)			
n	292	289	581
Mean (SD)	5.78 (1.422)	5.80 (1.410)	5.79 (1.415)
Median	6.50	6.50	6.50
25th / 75th Percentile	6.00, 6.50	6.00, 6.50	6.00, 6.50
Min, Max	0.5, 6.5	0.5, 6.5	0.5, 6.5
Ranibizumab Treatment Duration (days)			
n	292	289	581
Mean (SD)	311.9 (78.44)	312.3 (78.11)	312.1 (78.21)
Median	337.0	337.0	337.0
25th / 75th Percentile	334.0, 342.0	333.0, 340.0	333.0, 342.0
Min, Max	1, 398	1, 397	1, 398

Note: Presented statistics are based on subjects in the Safety Set the actual treatment received group.
Cross-reference: Listing 16.2.5.1
Table Generation: 21JAN2022 8:32 Program Name: t-14-03-04-03.sas

The full 52-week safety data set has been submitted in the D120 LoQ response package. The new data has been integrated into the full safety analysis.

A summary of treatment and study visit completion by treatment group and overall for the FAS is provided in Table 22.

All 292 subjects randomised to the Ximluci group were dosed with study drug.

A total of 290 subjects were randomised to the Lucentis group, of which 289 subjects were dosed with study drug; 1 subject in the Lucentis group withdrew consent and was not dosed with study drug.

A total of 96 subjects **(16.5%)** discontinued the study treatment early, including 47 subjects (16.1%) in the Ximluci group and 49 subjects (16.9%) in the Lucentis group.

The most common reason for early discontinuation of study treatment in both groups was subject request (ie, withdrawal of consent).

The mean (SD) treatment duration was similar between groups: 44.560 (11.2050) weeks in the

Ximluci group and 44.614 (11.1589) weeks in the Lucentis group.

Table 22: Treatment and Study Visit Completion (Full Analysis Set)

Subject Disposition	Xlucane N=292	Lucentis N=290	Overall N=582
Treatment Allocation, n (%)			
Dosed with Randomised Study Drug	292 (100)	289 (99.7)	581 (99.8)
Dosed with Non-Randomised Study Drug	0	0	0
Randomised Treatment Group = Actual Treatment Received Group	292 (100)	289 (99.7)	581 (99.8)
Treatment Completion, n (%)			
Completed Study Treatment Per Protocol	245 (83.9)	241 (83.1)	486 (83.5)
Early Discontinuation of Treatment	47 (16.1)	49 (16.9)	96 (16.5)
Subject request (ie, withdrawal of consent)	17 (5.8)	22 (7.6)	39 (6.7)
Use of nonpermitted concurrent therapy	1 (0.3)	0	1 (0.2)
Noncompliance with the study drug or study schedule	0	1 (0.3)	1 (0.2)
Lost to follow-up	4 (1.4)	6 (2.1)	10 (1.7)
Adverse event(s)	5 (1.7)	10 (3.4)	15 (2.6)
Investigator request	0	0	0
Intercurrent illness	0	0	0
Sponsor request	0	0	0
Treatment failure, as assessed by the treating investigator	1 (0.3)	1 (0.3)	2 (0.3)
Pregnancy	0	0	0
Death	4 (1.4)	1 (0.3)	5 (0.9)

Subject Disposition	Xlucane N=292	Lucentis N=290	Overall N=582
Other	15 (5.1)	8 (2.8)	23 (4.0)
Ongoing	0	0	0
Treatment Duration (Weeks)			
n	292	289	581
Mean (SD)	44.560 (11.2050)	44.614 (11.1589)	44.587 (11.1725)
Median	48.143	48.143	48.143
25th / 75th percentile	47.714, 48.857	47.571, 48.571	47.571, 48.857
Min, Max	0.14, 56.86	0.14, 56.71	0.14, 56.86
Study Visit Performed[a], n (%)			
Week 2	270 (92.5)	272 (93.8)	542 (93.1)
Week 4	282 (96.6)	277 (95.5)	559 (96.0)
Week 8	278 (95.2)	268 (92.4)	546 (93.8)
Week 12	275 (94.2)	265 (91.4)	540 (92.8)
Week 16	262 (89.7)	262 (90.3)	524 (90.0)
Week 20	262 (89.7)	255 (87.9)	517 (88.8)
Week 24	256 (87.7)	261 (90.0)	517 (88.8)
Week 28	253 (86.6)	254 (87.6)	507 (87.1)
Week 32	255 (87.3)	253 (87.2)	508 (87.3)
Week 36	249 (85.3)	256 (88.3)	505 (86.8)
Week 40	244 (83.6)	248 (85.5)	492 (84.5)
Week 44	246 (84.2)	242 (83.4)	488 (83.8)
Week 48	243 (83.2)	241 (83.1)	484 (83.2)
Week 52	246 (84.2)	241 (83.1)	487 (83.7)

Abbreviations: EOT, End of Treatment; FAS, full analysis set; Max, maximum; Min, minimum; SD, standard deviation.

[a] Weekly visits may include closest mapped EOT or unscheduled visits within the allowed protocol window if no weekly visit performed.

Note: Presented statistics, frequencies, and the denominator used for percentages are based on subjects in the FAS and the randomised treatment.

2.4.8.1. Adverse events

The proportion of subjects who had at least **1 ophthalmic TEAE** in the study eye was similar between the Ximluci group (105 subjects, 36.0%) and the Lucentis group (104 subjects, 36.0%). The majority of ophthalmic TEAEs in both treatment groups were mild in severity (Table 23).

In the Ximluci group, 23 subjects (7.9%) had ophthalmic TEAEs of moderate intensity and 4 subjects (1.4%) had ophthalmic TEAEs of severe intensity in the study eye. In the Lucentis group, 26 subjects (9.0%) had ophthalmic TEAEs of moderate intensity and 6 subjects (2.1%) had ophthalmic TEAEs of severe intensity in the study eye.

The proportion of subjects who had at least **1 ophthalmic study drug-related TEAE** in the study eye was similar between the Ximluci group (22 subjects [7.5%]; 29 events) and the Lucentis group (28 subjects [9.7%]; 41 events). Four subjects (1.4%) in the Ximluci group and 4 subjects (1.4%) in the Lucentis group experienced a **serious ophthalmic TEAE** in the study eye.

One subject (0.3%) in the Ximluci group and 2 subjects (0.7%) in the Lucentis group experienced an ophthalmic TEAE in the study eye that led to withdrawal of study drug.

The proportion of subjects who had at least 1 ophthalmic TEAE in the study eye that was associated with an injection site reaction was similar between the Ximluci (12.3%) and the Lucentis group (12.8%).

Table 23: Overall Summary of Treatment-emergent Adverse Events – Ophthalmic (Safety Set)

	XSB-001 DP N=292			Lucentis N=289			Overall N=581		
Category	**Study Eye n (%) #[AEs]**	**Fellow Eye n (%) #[AEs]**	**Both Eyes n (%) #[AEs]**	**Study Eye n (%) #[AEs]**	**Fellow Eye n (%) #[AEs]**	**Both Eyes n (%) #[AEs]**	**Study Eye n (%) #[AEs]**	**Fellow Eye n (%) #[AEs]**	**Both Eyes n (%) #[AEs]**
Subjects with at least 1 AE	107 (36.6) [166]	55 (18.8) [77]	18 (6.2) [20]	104 (36.0) [183]	55 (19.0) [82]	20 (6.9) [30]	211 (36.3) [349]	110 (18.9) [159]	38 (6.5) [50]
Subjects with at least 1 TEAE	105 (36.0) [164]	53 (18.2) [75]	17 (5.8) [19]	104 (36.0) [183]	54 (18.7) [81]	20 (6.9) [30]	209 (36.0) [347]	107 (18.4) [156]	37 (6.4) [49]
Mild	78 (26.7) [128]	36 (12.3) [54]	14 (4.8) [15]	72 (24.9) [132]	32 (11.1) [57]	16 (5.5) [26]	150 (25.8) [260]	68 (11.7) [111]	30 (5.2) [41]
Moderate	23 (7.9) [30]	14 (4.8) [17]	2 (0.7) [2]	26 (9.0) [43]	19 (6.6) [21]	4 (1.4) [4]	49 (8.4) [73]	33 (5.7) [38]	6 (1.0) [6]
Severe	4 (1.4) [6]	3 (1.0) [4]	1 (0.3) [2]	6 (2.1) [8]	3 (1.0) [3]	0	10 (1.7) [14]	6 (1.0) [7]	1 (0.2) [2]
Related to study drug	22 (7.5) [29]	0	0	28 (9.7) [41]	0	0	50 (8.6) [70]	0	0
Mild	17 (5.8) [24]	0	0	17 (5.9) [26]	0	0	34 (5.9) [50]	0	0
Moderate	5 (1.7) [5]	0	0	9 (3.1) [13]	0	0	14 (2.4) [18]	0	0
Severe	0	0	0	2 (0.7) [2]	0	0	2 (0.3) [2]	0	0
Subjects with at least 1 SAE	4 (1.4) [4]	0	0	4 (1.4) [5]	0	0	8 (1.4) [9]	0	0

	XSB-001 DP N=292			Lucentis N=289			Overall N=581		
Category	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]
Subjects with at least 1 serious TEAE	4 (1.4) [4]	0	0	4 (1.4) [5]	0	0	8 (1.4) [9]	0	0
Related to study drug	2 (0.7) [2]	0	0	2 (0.7) [3]	0	0	4 (0.7) [5]	0	0
Subjects with at least 1 TEAE leading to withdrawal of study drug	1 (0.3) [1]	0	0	2 (0.7) [2]	0	0	3 (0.5) [3]	0	0
Subjects with at least 1 TEAE associated with an injection site reaction	36 (12.3) [48]	0	0	37 (12.8) [51]	1 (0.3) [1]	1 (0.3) [1]	73 (12.6) [99]	1 (0.2) [1]	1 (0.2) [1]

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Notes: Multiple TEAEs for a subject are only counted once within the respective n according to the maximum severity and/or relationship to study drug recorded. The #AEs includes every relevant adverse event. If severity was missing or unknown then severity was derived as severe. If relationship to study drug for a TEAE was missing then relationship to study drug was derived as related. Presented frequencies and the denominator used for percentages are based on subjects in the Safety Set and the actual treatment received group.

Common and Non-serious adverse events

A summary of **ophthalmic TEAEs (reported in >1% of subjects)** in either treatment group in the study eye) by SOC and PT for the SS is presented in Table 24.

The proportion of subjects who had at least 1 ophthalmic TEAE in the study eye was overall similar between the Ximluci (105 subjects [36.0%]; 164 events) and the Lucentis group (104 subjects [36.0%]; 183 events). The most common ophthalmic TEAE in the study eye in both treatment groups was conjunctival haemorrhage, which was reported in 15 subjects (5.1%) in the Ximluci group and 16 subjects (5.5%) in the Lucentis group. The other most commonly reported ophthalmic TEAEs in the study eye (reported in ≥10 subjects overall) included visual acuity reduced, retinal haemorrhage, retinal pigment epithelial tear, vitreous floaters, vitreous detachment, and visual impairment.

The Applicant was asked to further discuss the topic of subretinal fluid and, based on their evaluation, to comment on the need to update the product information with this ADR. Twice as many patients were reported as having subretinal fluid in the Ximluci group (n=6, 2.1%) compared with n=3 (1.0%) for Lucentis. 1 of the subjects in the Ximluci group had a non-serious ophthalmic TEAE of moderate subretinal fluid in the study eye that led to withdrawal of study drug; the event was considered by the investigator to be related to study drug. This is not a listed ADR for Lucentis, although 'retinal disorders' are generally included. The Applicant does not consider an update to the product information with the ADR subretinal fluid is required, on the basis of the justification provided with the responses and given the demonstration of similarity to Lucentis, a significant difference in ADR profile is not plausible. Rather the Applicant provided their rationale behind the conclusion that the numerical difference in ADRs reporting subretinal fluid are likely to be a chance finding. Baseline ocular factors in the Ximluci treatment group may also have contributed to this finding.

The Applicant's response is considered acceptable. It is recommended that this ADR should continue to be monitored through routine pharmacovigilance.

Table 24: Summary of Ophthalmic Treatment-emergent Adverse Events Reported in >1% of Subjects in Either Treatment Group in the Study Eye by System Organ Class and Preferred Term (Safety Set)

	XSB-001 DP N=292			Lucentis N=289			Overall N=581		
SOC/ PT	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]
Subjects with at least 1 TEAE	**105 (36.0) [164]**	**53 (18.2) [75]**	**17 (5.8) [19]**	**104 (36.0) [183]**	**54 (18.7) [81]**	**20 (6.9) [30]**	**209 (36.0) [347]**	**107 (18.4) [156]**	**37 (6.4) [49]**
Eye disorders	**97 (33.2) [152]**	**47 (16.1) [67]**	**15 (5.1) [17]**	**95 (32.9) [160]**	**45 (15.6) [68]**	**14 (4.8) [23]**	**192 (33.0) [312]**	**92 (15.8) [135]**	**29 (5.0) [40]**
Conjunctival haemorrhage	15 (5.1) [19]	1 (0.3) [4]	0	16 (5.5) [22]	1 (0.3) [1]	0	31 (5.3) [41]	2 (0.3) [5]	0
Visual acuity reduced	8 (2.7) [8]	2 (0.7) [3]	0	8 (2.8) [10]	2 (0.7) [3]	0	16 (2.8) [18]	4 (0.7) [6]	0
Retinal haemorrhage	7 (2.4) [7]	1 (0.3) [1]	0	8 (2.8) [9]	2 (0.7) [2]	0	15 (2.6) [16]	3 (0.5) [3]	0
Retinal pigment epithelial tear	6 (2.1) [6]	0	0	7 (2.4) [8]	0	0	13 (2.2) [14]	0	0
Vitreous floaters	5 (1.7) [5]	2 (0.7) [2]	0	8 (2.8) [8]	0	0	13 (2.2) [13]	2 (0.3) [2]	0
Vitreous detachment	8 (2.7) [8]	2 (0.7) [2]	1 (0.3) [1]	4 (1.4) [4]	1 (0.3) [1]	0	12 (2.1) [12]	3 (0.5) [3]	1 (0.2) [1]
Visual impairment	5 (1.7) [5]	2 (0.7) [2]	1 (0.3) [1]	6 (2.1) [6]	2 (0.7) [2]	0	11 (1.9) [11]	4 (0.7) [4]	1 (0.2) [1]
Subretinal fluid	6 (2.1) [6]	0	0	3 (1.0) [3]	0	0	9 (1.5) [9]	0	0
Macular degeneration	5 (1.7) [5]	2 (0.7) [2]	1 (0.3) [1]	3 (1.0) [3]	0	0	8 (1.4) [8]	2 (0.3) [2]	1 (0.2) [1]
Cataract	3 (1.0) [4]	1 (0.3) [1]	0	4 (1.4) [4]	5 (1.7) [5]	2 (0.7) [2]	7 (1.2) [8]	6 (1.0) [6]	2 (0.3) [2]
Subretinal fibrosis	4 (1.4) [4]	0	0	3 (1.0) [3]	1 (0.3) [1]	1 (0.3) [1]	7 (1.2) [7]	1 (0.2) [1]	1 (0.2) [1]
Blepharitis	4 (1.4) [4]	3 (1.0) [3]	3 (1.0) [3]	2 (0.7) [3]	2 (0.7) [3]	2 (0.7) [3]	6 (1.0) [7]	5 (0.9) [6]	5 (0.9) [6]
Eye pain	2 (0.7) [2]	0	0	4 (1.4) [4]	0	0	6 (1.0) [6]	0	0
Epiretinal membrane	4 (1.4) [4]	1 (0.3) [1]	0	1 (0.3) [1]	1 (0.3) [1]	0	5 (0.9) [5]	2 (0.3) [2]	0
Neovascular age-related macular degeneration	0	11 (3.8) [11]	0	4 (1.4) [5]	12 (4.2) [12]	0	4 (0.7) [5]	23 (4.0) [23]	0
Ocular hypertension	0	0	0	4 (1.4) [4]	3 (1.0) [3]	3 (1.0) [3]	4 (0.7) [4]	3 (0.5) [3]	3 (0.5) [3]

	XSB-001 DP N=292			Lucentis N=289			Overall N=581		
SOC/ PT	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]
Infections and infestations	**5 (1.7) [5]**	**4 (1.4) [4]**	**1 (0.3) [1]**	**9 (3.1) [10]**	**6 (2.1) [6]**	**4 (1.4) [4]**	**14 (2.4) [15]**	**10 (1.7) [10]**	**5 (0.9) [5]**
Conjunctivitis	1 (0.3) [1]	2 (0.7) [2]	0	7 (2.4) [7]	4 (1.4) [4]	4 (1.4) [4]	8 (1.4) [8]	6 (1.0) [6]	4 (0.7) [4]
Investigations	**2 (0.7) [2]**	**0**	**0**	**6 (2.1) [7]**	**5 (1.7) [5]**	**2 (0.7) [2]**	**8 (1.4) [9]**	**5 (0.9) [5]**	**2 (0.3) [2]**
Intraocular pressure increased	2 (0.7) [2]	0	0	6 (2.1) [7]	5 (1.7) [5]	2 (0.7) [2]	8 (1.4) [9]	5 (0.9) [5]	2 (0.3) [2]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: Descriptions of TEAEs were coded using MedDRA version 23.0. Presented frequencies and the denominator used for percentages were based on subjects in the Safety Set and the actual treatment received group. Subjects with multiple TEAEs within the same SOC and/or PT were only counted once within the respective n. The #AEs included every relevant AE.

Non-ophthalmic TEAEs

An overall summary of **non-ophthalmic TEAEs** for the SS is presented in Table 25.

The proportion of subjects who had at least 1 non-ophthalmic TEAE was slightly higher in the Lucentis group (153 subjects [52.9%]; 373 events) compared to the Ximluci group (134 subjects [45.9%]; 295 events).

The majority of non-ophthalmic TEAEs in both treatment groups were mild or moderate in severity. Two subjects in each group had a non-ophthalmic study drug-related TEAE.

Non-ophthalmic SAEs were reported in **29 subjects (9.9%)** in the Ximluci group and **31 subjects (10.7%)** in the Lucentis group. All non-ophthalmic SAEs in the Ximluci group were considered by the investigator to be not related to study drug. In the Lucentis group, 1 non-ophthalmic SAE of myocardial infarction was considered by the investigator to be related to study drug, all other non-ophthalmic SAEs were considered by the investigator to be not related to study drug.

Two subjects (0.7%) in the Ximluci group and 5 subjects (1.7%) in the Lucentis group experienced a non-ophthalmic TEAE that led to withdrawal of study drug.

Table 25: Overall Summary of Treatment-emergent Adverse Events – Non-Ophthalmic (Safety Set)

Category	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Subjects with at least 1 AE	139 (47.6) [305]	156 (54.0) [386]	295 (50.8) [691]
Subjects with at least 1 TEAE	134 (45.9) [295]	153 (52.9) [373]	287 (49.4) [668]
Mild	70 (24.0) [167]	78 (27.0) [226]	148 (25.5) [393]
Moderate	46 (15.8) [101]	54 (18.7) [119]	100 (17.2) [220]
Severe	18 (6.2) [27]	21 (7.3) [28]	39 (6.7) [55]
Related to study drug	2 (0.7) [2]	2 (0.7) [2]	4 (0.7) [4]
Mild	2 (0.7) [2]	1 (0.3) [1]	3 (0.5) [3]
Moderate	0	0	0
Severe	0	1 (0.3) [1]	1 (0.2) [1]
Subjects with at least 1 SAE	29 (9.9) [52]	31 (10.7) [41]	60 (10.3) [93]
Subjects with at least 1 serious TEAE	28 (9.6) [51]	31 (10.7) [41]	59 (10.2) [92]
Related to study drug	0	1 (0.3) [1]	1 (0.2) [1]
Subjects with at least 1 TEAE leading to withdrawal of study drug	2 (0.7) [3]	5 (1.7) [8]	7 (1.2) [11]
Subjects with at least one TEAE associated with an injection site reaction	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Notes: Multiple TEAEs for a subject are only counted once within the respective n according to the maximum severity and/or relationship to study drug recorded. The #AEs includes every relevant adverse event. If severity was missing or unknown then severity was derived as severe. If relationship to study drug for a TEAE was missing then relationship to study drug was derived as related. Presented frequencies and the denominator used for percentages are based on subjects in the Safety Set and the actual treatment received group.

A summary of **non-ophthalmic TEAEs** (reported in >1% of subjects in either treatment group) by SOC and PT for the SS is presented in Table 26.

The most commonly reported non-ophthalmic TEAEs (reported in ≥10 subjects overall) included hypertension, COVID-19, hypercholesterolaemia, nasopharyngitis, headache, urinary tract infection, and atrial fibrillation.

Table 26: Summary of Non-Ophthalmic Treatment-emergent Adverse Events Reported in >1% of Subjects in Either Treatment Group by System Organ Class and Preferred Term (Safety Set)

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Subjects with at least 1 TEAE	**134 (45.9) [295]**	**153 (52.9) [373]**	**287 (49.4) [668]**
Infections and infestations	**42 (14.4) [55]**	**49 (17.0) [53]**	**91 (15.7) [108]**
COVID-19	11 (3.8) [11]	8 (2.8) [8]	19 (3.3) [19]
Nasopharyngitis	7 (2.4) [7]	6 (2.1) [7]	13 (2.2) [14]
Urinary tract infection	10 (3.4) [13]	2 (0.7) [2]	12 (2.1) [15]
Pneumonia	5 (1.7) [5]	2 (0.7) [2]	7 (1.2) [7]
Gastrointestinal disorders	**14 (4.8) [16]**	**29 (10.0) [43]**	**43 (7.4) [59]**
Diarrhoea	4 (1.4) [4]	5 (1.7) [5]	9 (1.5) [9]
Gastrooesophageal reflux disease	0	5 (1.7) [5]	5 (0.9) [5]
Dyspepsia	0	4 (1.4) [4]	4 (0.7) [4]
Metabolism and nutrition disorders	**15 (5.1) [17]**	**28 (9.7) [39]**	**43 (7.4) [56]**
Hypercholesterolaemia	6 (2.1) [6]	9 (3.1) [11]	15 (2.6) [17]
Musculoskeletal and connective tissue disorders	**22 (7.5) [29]**	**19 (6.6) [25]**	**41 (7.1) [54]**
Back pain	5 (1.7) [6]	4 (1.4) [4]	9 (1.5) [10]
Osteoarthritis	5 (1.7) [6]	2 (0.7) [2]	7 (1.2) [8]
Pain in extremity	1 (0.3) [2]	6 (2.1) [6]	7 (1.2) [8]
Arthralgia	4 (1.4) [4]	2 (0.7) [2]	6 (1.0) [6]
Investigations	**16 (5.5) [20]**	**22 (7.6) [31]**	**38 (6.5) [51]**
Blood cholesterol increased	2 (0.7) [2]	7 (2.4) [7]	9 (1.5) [9]
Blood triglycerides increased	5 (1.7) [6]	2 (0.7) [2]	7 (1.2) [8]
Blood pressure increased	1 (0.3) [1]	4 (1.4) [4]	5 (0.9) [5]
Nervous system disorders	**17 (5.8) [23]**	**21 (7.3) [25]**	**38 (6.5) [48]**
Headache	5 (1.7) [6]	8 (2.8) [8]	13 (2.2) [14]
Vascular disorders	**18 (6.2) [18]**	**20 (6.9) [27]**	**38 (6.5) [45]**
Hypertension	10 (3.4) [10]	17 (5.9) [19]	27 (4.6) [29]

Injury, poisoning and procedural complications	**18 (6.2) [35]**	**13 (4.5) [17]**	**31 (5.3) [52]**
Fall	5 (1.7) [6]	4 (1.4) [5]	9 (1.5) [11]
Cardiac disorders	**10 (3.4) [11]**	**13 (4.5) [19]**	**23 (4.0) [30]**
Atrial fibrillation	5 (1.7) [5]	5 (1.7) [6]	10 (1.7) [11]
General disorders and administration site conditions	**11 (3.8) [12]**	**5 (1.7) [5]**	**16 (2.8) [17]**
Pyrexia	4 (1.4) [4]	4 (1.4) [4]	8 (1.4) [8]
Ear and labyrinth disorders	**4 (1.4) [4]**	**10 (3.5) [14]**	**14 (2.4) [18]**
Vertigo	2 (0.7) [2]	7 (2.4) [10]	9 (1.5) [12]
Blood and lymphatic system disorders	**2 (0.7) [2]**	**9 (3.1) [12]**	**11 (1.9) [14]**
Anaemia	0	4 (1.4) [4]	4 (0.7) [4]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: Descriptions of TEAEs were coded using MedDRA version 23.0. Presented frequencies and the denominator used for percentages were based on subjects in the Safety Set and the actual treatment received group. Subjects with multiple TEAEs within the same SOC and/or PT were only counted once within the respective n. The #AEs included every relevant AE.

A total of 4 subjects (2 subjects in each treatment group) experienced a **non-ophthalmic treatment-related TEAE** (Table 27).

In the Ximluci group, 1 subject (0.3%) experienced a treatment-related non-serious TEAE of mild myocardial ischaemia and 1 subject (0.3%) experienced a treatment-related non-serious TEAE of mild eosinophil count increased.

The applicant was asked to provide an explanation regarding the assessment of this event of "mild myocardial ischaemia". Following assessment of the Applicant's response, it is concluded that this does not comply with any of the severity criteria to be considered a serious adverse event given that this event did not lead the patient to hospitalization, did not require extensive procedural or an extensive drug treatment, and was not life-threatening. The dose of the study drug was not changed neither.

In the Lucentis group, 1 subject (0.3%) experienced a treatment-related serious TEAE of severe myocardial infarction and 1 subject (0.3%) experienced a treatment-related non-serious TEAE of mild liver function test increased.

Table 27: Summary of Non-Ophthalmic Treatment-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Subjects with at least 1 treatment-related TEAE	2 (0.7) [2]	2 (0.7) [2]	4 (0.7) [4]
Cardiac disorders	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Myocardial infarction	0	1 (0.3) [1]	1 (0.2) [1]
Myocardial ischaemia	1 (0.3) [1]	0	1 (0.2) [1]
Investigations	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Eosinophil count increased	1 (0.3) [1]	0	1 (0.2) [1]
Liver function test increased	0	1 (0.3) [1]	1 (0.2) [1]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: Descriptions of TEAEs were coded using MedDRA version 23.0. If relationship to study drug for a TEAE was missing then relationship to study drug was derived as related. Subjects with multiple TEAEs within the same SOC and/or PT were only counted once within the respective n. The #AEs included every relevant AE. Presented frequencies and the denominator used for percentages were based on subjects in the Safety Set and the actual treatment received group.

2.4.8.2. Serious adverse event/deaths/other significant events

A total of 8 subjects (1.4%) had ophthalmic **SAEs** in the study eye during the study (4 subjects [1.4%] in the Ximluci group and 4 subjects [1.4%] in the Lucentis group).
No subjects experienced ophthalmic SAEs in the fellow eye.

A summary of ophthalmic SAEs by SOC and PT for the SS is presented in the table below. All ophthalmic SAEs were also serious TEAEs and are presented.

In the XSB-001 DP (Ximluci) group, 4 subjects (0.7%) experienced ophthalmic SAEs in the study eye.

- Subject [redacted]ed an SAE of retinal haemorrhage (verbatim term: **subretinal haemorrhage** in study eye) of severe intensity on 14 May 2020. The event was considered an SAE because it resulted in persistent or significant disability/incapacity. No action was taken with the study drug due to the SAE. The SAE was considered recovered/resolved with sequelae on 20 Aug 2020. The event of retinal haemorrhage was considered by the investigator to be not related to study drug.
- Subject [redacted]ed an SAE of **retinal pigment epithelial tear** (verbatim term: retina pigment epithelium rip) of moderate intensity on an unspecified day in Mar 2020. The event was an SAE because it was considered to be an important medical event. No action was taken with the study drug due to the SAE. At the time of the interim analysis data snapshot, the event was considered not recovered/not resolved. **The event of retinal pigment epithelial tear was considered by the investigator to be related to study drug.**
- Subject [redacted]ed an SAE of **macular vasospasm** (verbatim term: spasm of arterial macular vessel) of moderate intensity on 14 December 2020. The event was considered an SAE because it required hospitalization and was considered an important medical event. Action taken with the study drug due to the SAE was not applicable. The SAE was considered recovered/resolved with sequelae on 18 December 2020. The event of macular vasospasm was considered by the investigator to be not related to study drug.

- Subject [redacted]ed an SAE of **retinal pigment epithelial tear** (verbatim term: retinal pigment epithelial [RPE] rip, also referred to as a RPE tear) of mild intensity on 02 October 2020. The event was an SAE because it was considered to be an important medical event. No action was taken with the study drug due to the SAE. At the time of final database lock, the event was considered not recovered/not resolved. **The event of retinal pigment epithelial tear was considered by the investigator to be related to study drug.**

In the Lucentis group, 4 subjects (1.4%) experienced ophthalmic SAEs in the study eye.

- Subject [redacted]ed an SAE of **retinal haemorrhage** (verbatim term: subretinal haemorrhage) of moderate intensity on 26 Oct 2020. No action was taken with the study drug because of the event. The SAE was considered recovered/resolved with sequelae on 15 Mar 2021. The event of retinal haemorrhage was considered by the investigator to be not related to study drug.
- Subject [redacted]ed an SAE of **retinal pigment epithelial tear** (verbatim term: retina pigment epithelium tear) of severe intensity on 30 Jan 2020. No action was taken with the study drug because of the event. The SAE was considered recovered/resolved with sequelae on 19 Jun 2020. **The event of retinal pigment epithelial tear was considered by the investigator to be related to study drug.**

  Subject [redacted]ed an SAE of **visual acuity reduced** (verbatim term: VA decrease) of severe intensity on 20 Oct 2020. No action was taken with the study drug because of the event. The SAE was considered recovered/resolved with sequelae on 15 Nov 2020. The event of visual acuity reduced was considered by the investigator to be not related to study drug.

  Subject [redacted]ed an SAE of **endophthalmitis** (verbatim term: endophthalmitis) of severe intensity on 17 Mar 2020. The event was considered an SAE because it resulted in persistent or significant disability/incapacity. Study drug was withdrawn because of the event. The SAE was considered recovered/resolved with sequelae on 26 Mar 2020. **The event of endophthalmitis was considered by the investigator to be related to study drug.**

A summary of ophthalmic SAEs by SOC and PT for the SS are presented in Table 28.

Table 28: Summary of Ophthalmic Serious Adverse Events by System Organ Class and Preferred Term (Safety Set)

	XSB-001 DP N=292			Lucentis N=289			Overall N=581		
SOC/ PT	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]	Study Eye n (%) #[AEs]	Fellow Eye n (%) #[AEs]	Both Eyes n (%) #[AEs]
Subjects with at least 1 SAE	**4 (1.4) [4]**	**0**	**0**	**4 (1.4) [5]**	**0**	**0**	**8 (1.4) [9]**	**0**	**0**
Eye disorders	**4 (1.4) [4]**	**0**	**0**	**3 (1.0) [4]**	**0**	**0**	**7 (1.2) [8]**	**0**	**0**
Retinal pigment epithelial tear	2 (0.7) [2]	0	0	1 (0.3) [2]	0	0	3 (0.5) [4]	0	0
Retinal haemorrhage	1 (0.3) [1]	0	0	1 (0.3) [1]	0	0	2 (0.3) [2]	0	0
Macular vasospasm	1 (0.3) [1]	0	0	0	0	0	1 (0.2) [1]	0	0
Visual acuity reduced	0	0	0	1 (0.3) [1]	0	0	1 (0.2) [1]	0	0
Infections and infestations	**0**	**0**	**0**	**1 (0.3) [1]**	**0**	**0**	**1 (0.2) [1]**	**0**	**0**
Endophthalmitis	0	0	0	1 (0.3) [1]	0	0	1 (0.2) [1]	0	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

Notes: Descriptions of SAEs were coded using MedDRA version 23.0. Subjects with multiple SAEs within the same SOC and/or PT were only counted once within the respective n. The #AEs included every relevant AE. Presented frequencies and the denominator used for percentages were based on subjects in the Safety Set and the actual treatment received group.

Source: Xplore CSR Table 14.3.1.4.1

Fatal cases

A total of **11 subjects** died during the 52 week study period (8 subjects in the Ximluci group and 3 subjects in the Lucentis group). None of the deaths were considered by the investigator to be related to the study drug. A total of 3 subjects died during the first 6 months of the study.

In the Ximluci group, a total of **8 subjects** died over 52 week treatment period.

Subject [redacted]rdiopulmonary failure (verbatim term: acute heart and pulmonary insufficiency), which was considered by the investigator to be not related to study drug.

Subject [redacted]VID-19 (verbatim term: COVID-19 infection) and respiratory distress, which were considered by the investigator to be not related to study drug.

Subject [redacted]**known cause,** the death was considered by the investigator to be not related to study drug.

Subject [redacted] 69-year-old White male diagnosed with neovascular age-related macular degeneration in the right eye (OD), was randomly assigned to receive Xlucane (0.05 mL of 10 mg/mL ranibizumab). His other ophthalmologic history included cataract in both eyes (OU) and dry age-related macular degeneration in the left eye (OS). His medical/surgical history included angina pectoris, myocardial fibrosis, hypercholesterolaemia, type 2 diabetes mellitus, glomerulonephritis chronic, and hypertension. Concomitant medications included metformin, metoprolol, amlodipine, enalapril, gliclazide, and acetylsalicylic acid.

The subject received his first dose of Xlucane on 23 JAN 2020 (Study Day 1), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the right eye (OD). The subject received his most recent dose of Xlucane before the event on 06 JUL 2020 (Study Day 166), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the right eye (OD).

On 06 JUL 2020 (Study Day 166), the subject experienced hypercreatininaemia (hypercreatininemia) of moderate intensity. No treatment details were reported. The event was ongoing at the time of death of the subject. On 23 SEP 2020 (Study Day 245), the subject died (death; death [unknown cause]). Per the CIOMS report, on 23 SEP 2020 (Study Day 245), the subject died because of an unknown cause. It was unknown whether an autopsy was performed. No additional details were available.

Action taken with the study drug was not applicable because of the event of death. The subject was withdrawn from the study on 23 SEP 2020 (Study Day 245) because of the event.

Subject [redacted]diac arrest, which was considered by the investigator to be not related to study drug.

Subject [redacted] 76-year-old White male diagnosed with neovascular age-related macular degeneration in the left eye (OS), was randomly assigned to receive Xlucane (0.05 mL of 10 mg/mL ranibizumab). His other ophthalmologic history included cataract in both eyes (OU). His medical/surgical history included hypertension, arrhythmia, atrial fibrillation, myocardial infarction, osteoarthritis, peripheral venous disease, and coronary arterial stent insertion. Concomitant medications included ramipril, dabigatran etexilate, amiloride/hydrochlorothiazide, diosmin/hesperidin, metoprolol, and amlodipine.

The subject received his first dose of Xlucane on 29 JUN 2020 (Study Day 1), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the left eye (OS). The subject received his most recent and last dose of Xlucane before the event on 01 JUN 2021 (Study Day 338), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the left eye (OS).

On 24 JUN 2021 (Study Day 361), the subject experienced cardiac arrest of severe intensity. Per the CIOMS report, according to the subject's life partner, on 24 JUN 2021 (Study Day 361), the subject died because of cardiac arrest. No additional information was available. An autopsy was performed. The outcome of the event of cardiac arrest was "fatal."

No treatment was reported for the event.

Action taken with study drug because of the event of cardiac arrest was not applicable.

Subject [redacted]est pain and COVID-19 (verbatim term: SARS Cov-2 virus positivity), which were considered by the investigator to be not related to study drug.

Subject [redacted] 75-year-old White male diagnosed with neovascular age-related macular degeneration in the right eye (OD), was randomly assigned to receive Xlucane (0.05 mL of 10 mg/mL ranibizumab). His other ophthalmologic history included wet age-related macular degeneration in the right eye (OD), dry age-related macular degeneration in the left eye (OS), and hypermetropia in both eyes (OU). His medical/surgical history included myocardial ischaemia, venous thrombosis limb, benign prostatic hyperplasia, and percutaneous coronary intervention. Concomitant medications included acenocoumarol, amlodipine, tamsulosin, and finasteride.

The subject received his first dose of Xlucane on 14 JUL 2020 (Study Day 1) at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the right eye (OD). The subject received his most recent dose and last dose of Xlucane before the events on 03 FEB 2021 (Study Day 205) at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the right eye (OD).

On 25 FEB 2021 (Study Day 227), the subject experienced chest pain of severe intensity, and on 06 MAR 2021 (Study Day 236), the subject experienced COVID-19 (SARS Cov-2 virus) of severe intensity, both met the seriousness criterion of death. Per the CIOMS report, on 22 FEB 2021 (Study Day 224), the subject experienced an adverse event of chest pain of moderate intensity, which worsened to severe on 25 FEB 2021 (Study Day 227). On the same day (25 FEB 2021), the subject was hospitalized. On 25 FEB 2021 (Study Day 227), an ultrasonography showed 11 mm-thick pleural liquid on the right side, and later, on 26 FEB 2021 (Study Day 228), pleural liquid aspiration was carried out. On 03 MAR 2021 (Study Day 233), a

pleural liquid cytology showed a few mesothelial cells, macrophages, lymphocytes, and neutrophil granulocytes, but malignancy could not be confirmed.

On 06 MAR 2021 (Study Day 236), a SARS-CoV-2 polymerase chain reaction test was positive. Other laboratory test results on the same day (06 MAR 2021) showed mean corpuscular hemoglobin concentration of 30.9 g/dL (reference range [RR]: 31.8-35.4 g/dL), white blood cell count of 3.8 billion/L (RR: 4.6-10.2 billion/L), absolute eosinophil cell count of 0.009 billion/L (RR: 0.002-0.5 billion/L), platelet count of 118 g/L (RR: 142-424 g/L), serum potassium of 3.49 mmol/L (RR: 3.5-5.2 mmol/L), blood urea of 2.7 mmol/L (RR: 3.0-9.2 mmol/L), and C-reactive protein of 60.3 mg/L (RR: 0.0-5.0 mg/L).

On 11 MAR 2021 (Study Day 241), the laboratory test results showed lymphocyte count of 9.0% (RR: 10%-50%), absolute eosinophil cell count of 0.005 billion/L, activated partial thromboplastin time of 50.1 seconds (RR: 28-40 seconds), activated partial thromboplastin time ratio of 1.46 (RR: 0.81-1.16), gamma glutamyltransferase of 74 U/L (RR: 2-49 U/L), lactate dehydrogenase of 535 U/L (RR: 5-480 U/L), platelet count of 124 g/L, C-reactive protein of 249 mg/L, ferritin of 249 mg/L (RR: 28-365 mg/L), and absolute lymphocyte count of 0.659 billion/L (RR: 0.8-4.0 billion/L).

On 13 MAR 2021 (Study Day 243), the subject died. The cause of the death was reported as unknown. Per the investigator's assumption, the cause of death was COVID-19 pneumonia, but there were no available documents or other health records to confirm or disprove the assumption. It was unknown whether the autopsy was performed.

No treatment was reported for the events. The outcome of the events was "fatal".

The study drug was unchanged because of the events of chest pain and COVID-19.

The investigator assessed the SAEs as unrelated to the study drug and unrelated to the study drug injection procedure. Alternative causality for the event of chest pain was provided as pleural liquid. Alternative causality for the event of COVID-19 was not reported. The sponsor assessed the events as unrelated to the study drug.

The subject was discontinued early from the study on 13 MAR 2021 (Study Day 243).

Subject [redacted]esumed congestive heart failure; the subject had SAEs of urinary tract infection and arthralgia, which were considered by the investigator to be not related to study drug and had an outcome of fatal.

Subject [redacted] 78-year-old White male diagnosed with neovascular age-related macular degeneration in the right eye (OD), was randomly assigned to receive Xlucane (0.05 mL of 10 mg/mL ranibizumab). His other ophthalmologic history included dry age-related macular degeneration both eyes (OU). His medical/surgical history included gastrointestinal haemorrhage, type 2 diabetes mellitus, atrial fibrillation, hypertension, hyperchlorhydria, hypothyroidism, anaemia, prostate cancer, varicose vein, tonsillectomy, thyroidectomy, cardiac pacemaker insertion, and varicose vein operation. Concomitant medications included enoxaparin, esomeprazole, digoxin, propranolol, metformin, linagliptin, levothyroxine, thioctic acid, tamsulosin, ferrous/folic acid, and leuprorelin.

The subject received his first and most recent dose of Xlucane before the events on 09 SEP 2020 (Study Day 1), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the right eye (OD).

On 03 OCT 2020 (Study Day 25), the subject experienced sciatica (lumboischialgia) of moderate intensity. Per the CIOMS report, on 03 OCT 2020 (Study Day 25), the subject observed weakness in both legs accompanied by lumbar pain. On the same day, the subject was admitted to the hospital. On 08 OCT 2020 (Study Day 30), the results of a lumbar computed tomography scan showed discus hernia between L3-S1 and no radix compression.

The subject received tramadol 100 mg 4 times daily and fentanyl 25 µg every 3 days (both from 09 OCT 2020 to 19 OCT 2020) for the event of sciatica. Despite treatment with 4 doses of tramadol 100 mg, the subject suffered from unbearable pain.

On 09 OCT 2020 (Study Day 31), the subject experienced paraparesis (peripheral motor paraparesis) and urinary retention (urine retention), both of moderate intensity. Per the CIOMS report, on the same day, a transurethral catheter (bladder catheterization) was introduced as a drainage support because of the enlarged bladder. No treatment was reported for the events.

On 12 OCT 2020 (Study Day 34), the subject experienced pyrexia (fever) and staphylococcal infection (MRSA positivity), both of moderate intensity. Per the CIOMS report, on 12 OCT 2020 (Study Day 34), the subject had a fever of 38.7°C. Results of a hemoculture confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) positivity. The therapy was modified, and nasopharyngeal tests and another hemoculture were performed to confirm MRSA.

On 13 OCT 2020 (Study Day 35), an abdominal ultrasound showed 1 14-mm large cyst in the right kidney, 1 30-mm large cyst in the left kidney, and some small stones in the left kidney, which were not considered clinically significant; these were considered asymptomatic findings. On the same day, SARS-CoV-2 test results were negative.

On 16 Oct 2020 (Study Day 38), magnetic resonance imaging scan results showed that, from Th12 in the whole spinal canal, there was a space-occupying mass or pus with epidural or intradural spread.

The subject received amoxicillin/clavulanate 875/125 mg twice daily (12 OCT 2020 to 22 OCT 2020) for the event of pyrexia. The subject received sulfamethoxazole/trimethoprim 200 mg twice daily (12 OCT 2020 to 22 DEC 2020) and rifampicin 300 mg 3 times daily (12 OCT 2020 to ongoing) for the event of staphylococcal infection.

On 19 OCT 2020 (Study Day 41), the subject experienced schwannoma (intraspinal neurinoma) of moderate intensity. Per the CIOMS report, on 19 OCT 2020 (Study Day 41), the results of a magnetic resonance imaging scan showed neurinoma at L1 to L2, dislocating the conus and cauda fibers to the left. On the same day, neurosurgical interventions (flavectomy, spinal extra and intradural, intramedullary hemorrhage, and tumor excision) were performed. The intraspinal mass was found to consist of a tumor and hemorrhage, without abscess. The specimen was sent for histopathological examination. On the same day, treatment with vitamin D not otherwise specified 500 IU 5 times daily was started for prophylaxis.

On 16 NOV 2020 (Study Day 69), the subject experienced COVID-19 (COVID-19 positivity) of mild intensity. Per the CIOMS report, the subject had a SARS-CoV-2 polymerase chain reaction test, results of which showed COVID-19 positivity, and the subject was moved to a COVID department. On 30 NOV 2020 (Study Day 83), the subject was COVID-19 negative. The subject awaited to be transferred back for further physiotherapy. During his COVID-19 positivity, no symptoms related to this disease were observed. At that time, he was only receiving medication for MRSA positivity, and there were no changes to his medications. On 17 DEC 2020 (Study Day 100), a SARS-CoV-2 real-time polymerase chain reaction test showed negative results, but MRSA positivity was still present. On 22 DEC 2020 (Study Day 105), the subject was no longer MRSA positive and no longer taking sulfamethoxazole/trimethoprim. Otherwise, his medication remained unchanged.

On 08 FEB 2021 (Study Day 153), the subject's thyroid-stimulating hormone (TSH) level was 30.8238 mIU/L (reference range: 0.35-4.94 mIU/L). It was reported that the subject had been diagnosed with hypothyroidism ongoing since 2004. The subject was on medication (concomitant medication included levothyroxine) and had a normal T4 value and high TSH level; therefore, the elevated TSH condition was not considered an adverse event. On 10 MAR 2021 (Study Day 183), it was reported that the subject was using a urinary catheter to drain his bladder. The subject's treating physician tried to remove the catheter; however, because the bladder could not empty spontaneously, it was necessary to introduce the catheter again. No

further attempts were made to remove the catheter permanently. The regular physiotherapy was carried out, and the general status of the subject showed further improvement. The subject could now walk a short distance with a walking frame, but only a slight further improvement was observed in a week. No change in medications was made. The subject was transferred from a chronic internal medicine department to a musculoskeletal rehabilitation department.

On 06 MAY 2021 (Study Day 240), the subject was discharged from the hospital. From 06 MAY 2021, the event of urinary retention did not meet any further seriousness criteria; however, it continued as an ongoing condition requiring continuous use of urinary catheters to drain the bladder, which was viewed as a sequela of the serious event.

The subject received his most recent dose of Xlucane before the events of arthralgia and urinary tract infection on 22 JUN 2021 (Study Day 287), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the right eye (OD).

On 12 JUL 2021 (Study Day 307), the subject experienced arthralgia (joint pain) and urinary tract infection, both of severe intensity, which resulted in death. Per the CIOMS report, the subject suffered from joint pain and had bloody urine for around 10 days. The subject was hospitalized on 12 JUL 2021 (Study Day 307). The diagnosis of urinary tract infection was made because of a high C-reactive protein level and urine sedimentation. An abdominal ultrasound showed some choleliths with 5-17 mm diameter, 2 cysts in the left kidney, and enlarged prostate. An anteroposterior thoracic x-ray performed on the same day showed small amount of liquid in the sinuses, enlarged heart, enlarged central pulmonary vessels, and enlarged sclerotic aorta. The joint pain was most likely caused by the infection. The subject had a history of catheter use because of urinary retention.

During hospitalization, the subject received calcium chloride/potassium chloride/sodium acetate/sodium chloride, diuretics, antibiotics, and oxygen for the event of urinary tract infection; low molecular weight heparin and analgesics for the events of arthralgia and urinary tract infection (all from 12 JUL 2021 to 14 JUL 2021; doses and frequencies were not available).

On 14 JUL 2021 (Study Day 309), at 8 pm, the subject died because of arthralgia and urinary tract infection, without alarming signs. There were only limited diagnostic results available. According to the internists, the cause of death was congestive heart failure. The subject had no prior cardiac problems; the diagnosis was made based on the radiography performed on 12 JUL 2021 (Study Day 307). An autopsy was not performed, so it was presumed that the presence of urinary tract infection (possibly sepsis) was a direct cause of cardiac decompensation.

Relevant laboratory results are presented in the tables below.

The event of schwannoma was considered resolved with sequelae on 19 OCT 2020 (Study Day 41). The event of sciatica was considered resolved on 02 NOV 2020 (Study Day 55). The event of pyrexia was considered resolved on 10 NOV 2020 (Study Day 63). The event of COVID-19 was considered resolved on 30 NOV 2020 (Study Day 83). The event of staphylococcal infection was considered resolved on 22 DEC 2020 (Study Day 105). The events of paraparesis and urinary retention were considered resolved with sequelae on 06 MAY 2021 (Study Day 240). The sequela of the event of paraparesis was reported as inability to walk without walking frame. The subject's leg muscle strength improved a lot after the rehabilitation therapy. The event of urinary retention showed no improvement, and the subject required a urinary tract catheter, which was changed every 14 days. The outcome of arthralgia and urinary tract infection was fatal.

The study drug was unchanged because of the events of sciatica, paraparesis, urinary retention, pyrexia, staphylococcal infection, schwannoma, COVID-19, arthralgia, and urinary tract infection.

The investigator assessed all SAEs as unrelated to the study drug and unrelated to the study drug injection procedure. Alternative causality for the events of sciatica, paraparesis, and urinary retention was reported as Schwannoma, and alternative causalities for the event of pyrexia was reported as probably the Staphylococcal infection and COVID-19. Alternative causality for the events of staphylococcal infection, schwannoma, and COVID-19 was reported as unknown. The event of lumbar intraspinal abscess was a wrong diagnosis as it was a tumor and hemorrhage. Discus hernia was also reported as a wrong diagnosis. Alternate causality for the events of arthralgia and urinary tract infection was reported as presence of urinary tract catheter. The sponsor assessed all events as unrelated to the study drug.

The subject was discontinued early from the study on 14 JUL 2021 (Study Day 309).

Subject [redacted] **biological death (verbatim term: biological death),** which was considered by the investigator to be not related to study drug. The applicant was requested to provide further details on this case, the cause is listed as "biological death" which was not considered acceptable.

> Subject [redacted] an 84-year-old White female diagnosed with neovascular age-related macular degeneration in the left eye (OS), was randomly assigned to receive Xlucane (0.05 mL of 10 mg/mL ranibizumab). Her other ophthalmologic history included retinal neovascularisation in the left eye (OS), age-related macular degeneration in the right eye (OD), vitreous loss in both eyes (OU), intraocular lens implant in both eyes (OU), and cataract operation in both eyes (OU). Her medical/surgical history included menopause, bronchitis chronic, phlebitis, hypertension, and varicose vein operation. Concomitant medication included enalapril.
>
> The subject received her first dose of Xlucane on 31 JUL 2019 (Study Day 1), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the left eye (OS). The subject received her most recent and the last dose of Xlucane before the event on 21 JAN 2020 (Study Day 175), at a dose of 0.05 mL of 10 mg/mL ranibizumab administered intravitreally in the left eye (OS).
>
> On 18 FEB 2020 (Study Day 203), the subject died, which was considered as an SAE of death (biological death) of severe intensity. Per the CIOMS report, on 18 FEB 2020 (Study Day 203), the subject did not come to the scheduled study visit. Her daughter-in-law informed the site that the subject had suddenly fallen in the morning. Relatives called for emergency medical assistance, which confirmed the subject's biological death at 06:25 hours. The event of death met the seriousness criteria of a fatal event. The site did not have any information on symptoms and complaints before the subject's death. An autopsy was not performed. No additional details were available.
>
> No treatment was reported for the event. The event was considered fatal.

In the **Lucentis group**, **3 subjects** died.

Subject [redacted] ncreatitis acute (verbatim term: acute pancreatitis), which was considered by the investigator to be not related to study drug.

Subject [redacted] OVID-19 (verbatim term: COVID-19 confirmed severe acute respiratory syndrome), which was considered by the investigator to be not related to study drug.

Subject [redacted] ncreatitis acute (verbatim term: acute pancreatitis) and myocardial infarction, which were considered by the investigator to be not related to study drug.

Other Serious Events (SAEs)

Non-ophthalmic SAEs were reported in 29 subjects **(9.9%)** in the XSB-001 DP (Ximluci) group and 31 subjects **(10.7%)** in the Lucentis group. All non-ophthalmic SAEs in the XSB-001 DP (Ximluci) group were considered by the investigator to be not related to study drug. In the Lucentis group, 1 non-ophthalmic SAE of myocardial infarction was considered by the investigator to be related to study drug, all other non-ophthalmic SAEs were considered by the investigator to be not related to study drug.

A summary of Non-Ophthalmic Serious Adverse Events and a summary of Non-Ophthalmic Serious Treatment-Emergent Adverse Events by SOC and PT are presented in Table 29 and Table 30, respectively.

Table 29: Summary of Non-Ophthalmic Serious Adverse Events by System Organ Class and Preferred Term (Safety Set)

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Subjects with at least 1 SAE	**29 (9.9) [52]**	**31 (10.7) [41]**	**60 (10.3) [93]**
Infections and infestations	**7 (2.4) [13]**	**6 (2.1) [6]**	**13 (2.2) [19]**
COVID-19	5 (1.7) [5]	1 (0.3) [1]	6 (1.0) [6]
Pneumonia	2 (0.7) [2]	1 (0.3) [1]	3 (0.5) [3]
Urinary tract infection	3 (1.0) [3]	0	3 (0.5) [3]
Cellulitis	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Appendiceal abscess	0	1 (0.3) [1]	1 (0.2) [1]
COVID-19 pneumonia	0	1 (0.3) [1]	1 (0.2) [1]
Endocarditis	0	1 (0.3) [1]	1 (0.2) [1]
Gastroenteritis	1 (0.3) [1]	0	1 (0.2) [1]
Staphylococcal infection	1 (0.3) [1]	0	1 (0.2) [1]
Cardiac disorders	**6 (2.1) [7]**	**6 (2.1) [6]**	**12 (2.1) [13]**
Atrial fibrillation	3 (1.0) [3]	2 (0.7) [2]	5 (0.9) [5]
Myocardial infarction	0	3 (1.0) [3]	3 (0.5) [3]
Cardiac arrest	1 (0.3) [1]	0	1 (0.2) [1]
Cardiac failure	1 (0.3) [1]	0	1 (0.2) [1]
Cardiopulmonary failure	1 (0.3) [1]	0	1 (0.2) [1]
Myocardial ischaemia	0	1 (0.3) [1]	1 (0.2) [1]
Pericardial effusion	1 (0.3) [1]	0	1 (0.2) [1]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**4 (1.4) [5]**	**6 (2.1) [7]**	**10 (1.7) [12]**
Adenocarcinoma of colon	1 (0.3) [1]	0	1 (0.2) [1]
Anal cancer	1 (0.3) [1]	0	1 (0.2) [1]
Breast cancer	0	1 (0.3) [1]	1 (0.2) [1]
Bronchial carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Hodgkin's disease	0	1 (0.3) [1]	1 (0.2) [1]
Invasive breast carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Lung adenocarcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Lung neoplasm	1 (0.3) [1]	0	1 (0.2) [1]
Oesophageal carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Pancreatic carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Schwannoma	1 (0.3) [1]	0	1 (0.2) [1]
Vulval cancer	1 (0.3) [1]	0	1 (0.2) [1]

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Injury, poisoning and procedural complications	**6 (2.1) [6]**	**2 (0.7) [2]**	**8 (1.4) [8]**
Humerus fracture	3 (1.0) [3]	0	3 (0.5) [3]
Femur fracture	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Ankle fracture	0	1 (0.3) [1]	1 (0.2) [1]
Hip fracture	1 (0.3) [1]	0	1 (0.2) [1]
Incisional hernia	1 (0.3) [1]	0	1 (0.2) [1]
Respiratory, thoracic, and mediastinal disorders	**5 (1.7) [5]**	**3 (1.0) [3]**	**8 (1.4) [8]**
Chronic obstructive pulmonary disease	2 (0.7) [2]	0	2 (0.3) [2]
Dyspnoea	0	1 (0.3) [1]	1 (0.2) [1]
Epistaxis	0	1 (0.3) [1]	1 (0.2) [1]
Hiccups	1 (0.3) [1]	0	1 (0.2) [1]
Pleural effusion	1 (0.3) [1]	0	1 (0.2) [1]
Pulmonary oedema	0	1 (0.3) [1]	1 (0.2) [1]
Respiratory distress	1 (0.3) [1]	0	1 (0.2) [1]
Gastrointestinal disorders	**1 (0.3) [1]**	**6 (2.1) [6]**	**7 (1.2) [7]**
Inguinal hernia	0	2 (0.7) [2]	2 (0.3) [2]
Pancreatitis acute	0	2 (0.7) [2]	2 (0.3) [2]
Colonic haematoma	0	1 (0.3) [1]	1 (0.2) [1]
Intestinal obstruction	1 (0.3) [1]	0	1 (0.2) [1]
Strangulated umbilical hernia	0	1 (0.3) [1]	1 (0.2) [1]
General disorders and administration site conditions	**4 (1.4) [4]**	**1 (0.3) [1]**	**5 (0.9) [5]**
Death	2 (0.7) [2]	0	2 (0.3) [2]
Chest pain	1 (0.3) [1]	0	1 (0.2) [1]
Non-cardiac chest pain	0	1 (0.3) [1]	1 (0.2) [1]
Pyrexia	1 (0.3) [1]	0	1 (0.2) [1]
Nervous system disorders	**2 (0.7) [3]**	**2 (0.7) [2]**	**4 (0.7) [5]**
Transient ischaemic attack	0	2 (0.7) [2]	2 (0.3) [2]
Ischaemic stroke	1 (0.3) [1]	0	1 (0.2) [1]
Paraparesis	1 (0.3) [1]	0	1 (0.2) [1]
Sciatica	1 (0.3) [1]	0	1 (0.2) [1]
Renal and urinary disorders	**2 (0.7) [2]**	**2 (0.7) [2]**	**4 (0.7) [4]**
Acute kidney injury	1 (0.3) [1]	0	1 (0.2) [1]
End stage renal disease	0	1 (0.3) [1]	1 (0.2) [1]
Renal failure	0	1 (0.3) [1]	1 (0.2) [1]
Urinary retention	1 (0.3) [1]	0	1 (0.2) [1]

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Hepatobiliary disorders	**1 (0.3) [1]**	**2 (0.7) [2]**	**3 (0.5) [3]**
Cholecystitis	0	1 (0.3) [1]	1 (0.2) [1]
Cholecystitis chronic	1 (0.3) [1]	0	1 (0.2) [1]
Jaundice	0	1 (0.3) [1]	1 (0.2) [1]
Metabolism and nutrition disorders	**2 (0.7) [2]**	**1 (0.3) [1]**	**3 (0.5) [3]**
Dehydration	1 (0.3) [1]	0	1 (0.2) [1]
Hyperglycaemia	1 (0.3) [1]	0	1 (0.2) [1]
Hyponatraemia	0	1 (0.3) [1]	1 (0.2) [1]
Blood and lymphatic system disorders	**0**	**1 (0.3) [1]**	**1 (0.2) [1]**
Lymphadenopathy	0	1 (0.3) [1]	1 (0.2) [1]
Congenital, familial, and genetic disorders	**1 (0.3) [1]**	**0**	**1 (0.2) [1]**
Hypertrophic cardiomyopathy	1 (0.3) [1]	0	1 (0.2) [1]
Ear and labyrinth disorders	**0**	**1 (0.3) [1]**	**1 (0.2) [1]**
Vertigo	0	1 (0.3) [1]	1 (0.2) [1]
Musculoskeletal and connective tissue disorders	**1 (0.3) [1]**	**0**	**1 (0.2) [1]**
Arthralgia	1 (0.3) [1]	0	1 (0.2) [1]
Skin and subcutaneous tissue disorders	**1 (0.3) [1]**	**0**	**1 (0.2) [1]**
Dermatitis	1 (0.3) [1]	0	1 (0.2) [1]
Vascular disorders	**0**	**1 (0.3) [1]**	**1 (0.2) [1]**
Accelerated hypertension	0	1 (0.3) [1]	1 (0.2) [1]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

Notes: Descriptions of SAEs were coded using MedDRA version 23.0. Subjects with multiple SAEs within the same SOC and/or PT were only counted once within the respective n. The #AEs included every relevant AE. Presented frequencies and the denominator used for percentages were based on subjects in the Safety Set and the actual treatment received group.

Table 30: Summary of Non-Ophthalmic Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Subjects with at least 1 serious TEAE	**28 (9.6) [51]**	**31 (10.7) [41]**	**59 (10.2) [92]**
Infections and infestations	**7 (2.4) [13]**	**6 (2.1) [6]**	**13 (2.2) [19]**
COVID-19	5 (1.7) [5]	1 (0.3) [1]	6 (1.0) [6]
Pneumonia	2 (0.7) [2]	1 (0.3) [1]	3 (0.5) [3]
Urinary tract infection	3 (1.0) [3]	0	3 (0.5) [3]
Cellulitis	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Appendiceal abscess	0	1 (0.3) [1]	1 (0.2) [1]
COVID-19 pneumonia	0	1 (0.3) [1]	1 (0.2) [1]
Endocarditis	0	1 (0.3) [1]	1 (0.2) [1]
Gastroenteritis	1 (0.3) [1]	0	1 (0.2) [1]
Staphylococcal infection	1 (0.3) [1]	0	1 (0.2) [1]
Cardiac disorders	**6 (2.1) [7]**	**6 (2.1) [6]**	**12 (2.1) [13]**
Atrial fibrillation	3 (1.0) [3]	2 (0.7) [2]	5 (0.9) [5]
Myocardial infarction	0	3 (1.0) [3]	3 (0.5) [3]
Cardiac arrest	1 (0.3) [1]	0	1 (0.2) [1]
Cardiac failure	1 (0.3) [1]	0	1 (0.2) [1]
Cardiopulmonary failure	1 (0.3) [1]	0	1 (0.2) [1]
Myocardial ischaemia	0	1 (0.3) [1]	1 (0.2) [1]
Pericardial effusion	1 (0.3) [1]	0	1 (0.2) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (1.4) [5]**	**6 (2.1) [7]**	**10 (1.7) [12]**
Adenocarcinoma of colon	1 (0.3) [1]	0	1 (0.2) [1]
Anal cancer	1 (0.3) [1]	0	1 (0.2) [1]
Breast cancer	0	1 (0.3) [1]	1 (0.2) [1]
Bronchial carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Hodgkin's disease	0	1 (0.3) [1]	1 (0.2) [1]
Invasive breast carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Lung adenocarcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Lung neoplasm	1 (0.3) [1]	0	1 (0.2) [1]
Oesophageal carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Pancreatic carcinoma	0	1 (0.3) [1]	1 (0.2) [1]
Schwannoma	1 (0.3) [1]	0	1 (0.2) [1]
Vulval cancer	1 (0.3) [1]	0	1 (0.2) [1]

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Respiratory, thoracic, and mediastinal disorders	**5 (1.7) [5]**	**3 (1.0) [3]**	**8 (1.4) [8]**
Chronic obstructive pulmonary disease	2 (0.7) [2]	0	2 (0.3) [2]
Dyspnoea	0	1 (0.3) [1]	1 (0.2) [1]
Epistaxis	0	1 (0.3) [1]	1 (0.2) [1]
Hiccups	1 (0.3) [1]	0	1 (0.2) [1]
Pleural effusion	1 (0.3) [1]	0	1 (0.2) [1]
Pulmonary oedema	0	1 (0.3) [1]	1 (0.2) [1]
Respiratory distress	1 (0.3) [1]	0	1 (0.2) [1]
Gastrointestinal disorders	**1 (0.3) [1]**	**6 (2.1) [6]**	**7 (1.2) [7]**
Inguinal hernia	0	2 (0.7) [2]	2 (0.3) [2]
Pancreatitis acute	0	2 (0.7) [2]	2 (0.3) [2]
Colonic haematoma	0	1 (0.3) [1]	1 (0.2) [1]
Intestinal obstruction	1 (0.3) [1]	0	1 (0.2) [1]
Strangulated umbilical hernia	0	1 (0.3) [1]	1 (0.2) [1]
Injury, poisoning and procedural complications	**5 (1.7) [5]**	**2 (0.7) [2]**	**7 (1.2) [7]**
Humerus fracture	3 (1.0) [3]	0	3 (0.5) [3]
Femur fracture	1 (0.3) [1]	1 (0.3) [1]	2 (0.3) [2]
Ankle fracture	0	1 (0.3) [1]	1 (0.2) [1]
Incisional hernia	1 (0.3) [1]	0	1 (0.2) [1]
General disorders and administration site conditions	**4 (1.4) [4]**	**1 (0.3) [1]**	**5 (0.9) [5]**
Death	2 (0.7) [2]	0	2 (0.3) [2]
Chest pain	1 (0.3) [1]	0	1 (0.2) [1]
Non-cardiac chest pain	0	1 (0.3) [1]	1 (0.2) [1]
Pyrexia	1 (0.3) [1]	0	1 (0.2) [1]
Nervous system disorders	**2 (0.7) [3]**	**2 (0.7) [2]**	**4 (0.7) [5]**
Transient ischaemic attack	0	2 (0.7) [2]	2 (0.3) [2]
Ischaemic stroke	1 (0.3) [1]	0	1 (0.2) [1]
Paraparesis	1 (0.3) [1]	0	1 (0.2) [1]
Sciatica	1 (0.3) [1]	0	1 (0.2) [1]
Renal and urinary disorders	**2 (0.7) [2]**	**2 (0.7) [2]**	**4 (0.7) [4]**
Acute kidney injury	1 (0.3) [1]	0	1 (0.2) [1]
End stage renal disease	0	1 (0.3) [1]	1 (0.2) [1]
Renal failure	0	1 (0.3) [1]	1 (0.2) [1]
Urinary retention	1 (0.3) [1]	0	1 (0.2) [1]

SOC/ PT	XSB-001 DP N=292 n (%) #[AEs]	Lucentis N=289 n (%) #[AEs]	Overall N=581 n (%) #[AEs]
Hepatobiliary disorders	**1 (0.3) [1]**	**2 (0.7) [2]**	**3 (0.5) [3]**
Cholecystitis	0	1 (0.3) [1]	1 (0.2) [1]
Cholecystitis chronic	1 (0.3) [1]	0	1 (0.2) [1]
Jaundice	0	1 (0.3) [1]	1 (0.2) [1]
Metabolism and nutrition disorders	**2 (0.7) [2]**	**1 (0.3) [1]**	**3 (0.5) [3]**
Dehydration	1 (0.3) [1]	0	1 (0.2) [1]
Hyperglycaemia	1 (0.3) [1]	0	1 (0.2) [1]
Hyponatraemia	0	1 (0.3) [1]	1 (0.2) [1]
Blood and lymphatic system disorders	**0**	**1 (0.3) [1]**	**1 (0.2) [1]**
Lymphadenopathy	0	1 (0.3) [1]	1 (0.2) [1]
Congenital, familial and genetic disorders	**1 (0.3) [1]**	**0**	**1 (0.2) [1]**
Hypertrophic cardiomyopathy	1 (0.3) [1]	0	1 (0.2) [1]
Ear and labyrinth disorders	**0**	**1 (0.3) [1]**	**1 (0.2) [1]**
Vertigo	0	1 (0.3) [1]	1 (0.2) [1]
Musculoskeletal and connective tissue disorders	**1 (0.3) [1]**	**0**	**1 (0.2) [1]**
Arthralgia	1 (0.3) [1]	0	1 (0.2) [1]
Skin and subcutaneous tissue disorders	**1 (0.3) [1]**	**0**	**1 (0.2) [1]**
Dermatitis	1 (0.3) [1]	0	1 (0.2) [1]
Vascular disorders	**0**	**1 (0.3) [1]**	**1 (0.2) [1]**
Accelerated hypertension	0	1 (0.3) [1]	1 (0.2) [1]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: Descriptions of TEAEs were coded using MedDRA version 23.0. Subjects with multiple TEAEs within the same SOC and/or PT were only counted once within the respective n. The #AEs included every relevant AE. Presented frequencies and the denominator used for percentages were based on subjects in the Safety Set and the actual treatment received group.

Overdose

There were no documented cases of overdose. Based on the demonstration of biosimilarity, this application intends to rely on information for Lucentis prescribing information regarding overdose to support the safety of Ximluci (see below).

More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

2.4.8.3. Laboratory findings

Regarding the clinical chemistry, haematology and special test performed (such as slit lamp examination, dilated fundus examination, colour fundus photography and fluorescein angiography), the results from the 52 week data set are the same as in the interim analysis, no notable trends or differences between treatment groups were found.

Over the 52 weeks of the study, few subjects had a clinically significant abnormality in haematology (7 subjects in each treatment group) or clinical chemistry (31 subjects in the Ximluci groups versus 40 subjects in the Lucentis group) laboratory parameters.

In the same way, no notable trends in changes from baseline of vital signs or notable differences were observed between treatment groups.

Regarding the measurements of intraocular pressure, minimal changes from baseline were observed, and they were similar between the Ximluci and the Lucentis group.

In relation to IOP, the IOP measurements pre-injection and 30 minutes post-injection were similar between the Ximluci group and the Lucentis group at all-time points. A small increase in IOP (between 2 to 3 mmHg) was observed 30 minutes post-injection compared to pre-injection in both treatment groups. This is already known to occur with Lucentis and there were no differences identified in the Ximluci group.

There were no significant differences between both treatment groups over the 52 week data.

2.4.8.4. Immunological events

Immunogenicity was evaluated by anti-drug antibody (ADA) formation and neutralising antidrug antibody (NAb) up to Week 52 after Randomization. An electrochemiluminescence (ECL) bridging assay format that uses labelled (biotinylated and ruthenylated) XSB-001 was employed for screening, with confirmatory and titration tiers for ADA performed. The characterization of NAb was performed using a Competitive Ligand Binding Assay format (CLBA) that measured the capacity of the test samples to inhibit binding of XSB-001 to biotinylated VEGF-165 immobilized on streptavidin-coated plates.

In order to compare differences in the immunogenic responses between XSB-001 DP (Ximluci) and

Lucentis, serum samples were collected for evaluation of anti-drug antibody (ADA) and neutralizing anti-drug antibody (NAb) at baseline (Day 0) and weeks 4, 8, 12, 20, 24, 36, and 52.

The immunogenicity assessment encompassed all patients enrolled in the Xplore study.

Additional samples to those scheduled for routine immunogenicity testing were collected from patients with any sign of intraocular inflammation as they may indicate an immune reaction.

In line with the updated draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins, EMEA/CHMP/BMWP /14327/2006), immunogenicity was evaluated at baseline in order to preclude pre-existing Immunoreactivity.

The incidence rate of positive ADA and NAb results were similar in the two treatment arms. At baseline, the incidence of positive ADA was 12 subjects (4.2%) in the XSB-001 DP group and eight subjects (2.9%) in the Lucentis group.

At Week 24, the cumulative incidence of **positive ADA** was low in both treatment groups: 22 subjects (7.5%) in the XSB-001 DP group and 17 subjects (5.9%) in the Lucentis group. This numerically higher incidence of positive ADAs in the Ximluci group at week 24 when compared to the Lucentis arm had been noted. The applicant has since provided the outstanding immunogenicity data for both treatment groups from week 24 onwards and from this additional data there appears to be no notable differences in immunogenicity results between the XSB-001 DP and Lucentis groups over time. The potential for immunogenicity was observed to be low in the general Xplore study population. The incidence of positive results was low (≤ 7.5% of patients at any visit in the XSB- 001 DP (Ximluci) group compared with ≤11.9% in the Lucentis group).

At Week 52, the cumulative incidence of positive ADA was 33 subjects (11.3%) in the XSB-001 DP (Ximluci) group and 38 subjects (13.1%) in the Lucentis group.

The incidence of positive results was low (≤ 7.5% of patients at any visit in the XSB-001 DP (Ximluci) group compared with ≤11.9% in the Lucentis group).

Most of subjects were determined as ADA negative at each time point during the study. There were no notable differences in immunogenicity results between the XSB-001 DP (Ximluci) and Lucentis groups over time and the incidence of positive ADA was low and overall comparable between treatment groups.

Most detected ADA in the XSB-001 DP (Ximluci) and Lucentis treatment groups were non-neutralizing. Up to Week 50, no more than one patient had neutralizing antibodies and there was no obvious trend of a difference between treatment groups in terms of incidence at each time point.

Just as the cumulative incidence of positive ADA at Week 52, the incident of **neutralizing antibodies** was highest yet comparable between the treatment groups at 4/16 (25%) and 6/27 (22.2%) in XSB-001 DP and Lucentis group, respectively

A post-hoc analysis comparing subjects with positive ADA post baseline in subjects with negative ADA at baseline was similar between the groups and showed that 21 (7.7%) vs. 28 (10.5%) of subjects in Ximluci and Lucentis group, respectively, that were negative at baseline, at some point during the study tested positive for ADA.

A post-hoc analysis comparing the overall incidence of ophthalmic and non-ophthalmic treatment-emergent adverse events in subjects with positive ADA was similar between the treatment groups

The proportion of ADA positive subjects who had at least 1 ophthalmic TEAE in the study eye was lower in the Ximluci group (10 subjects, 30.3%) compared to the Lucentis group (15 subjects, 39.5%).

The majority of ophthalmic TEAEs in both treatment groups were mild in severity. In the Ximluci group, 3 ADA positive subjects (9.1%) had ophthalmic TEAEs of moderate intensity, while no ADA positive subjects had ophthalmic TEAEs of severe intensity in the study eye.

In the Lucentis group, 3 ADA positive subjects (7.9%) had ophthalmic TEAEs of moderate intensity and 1 ADA positive subject (2.6%) had ophthalmic TEAEs of severe intensity in the study eye

The proportion of ADA positive subjects who had at least 1 ophthalmic drug-related TEAE in the study eye was slightly higher in the Ximluci group (3 subjects [9.1%]; 5 events) compared to the Lucentis group (3 subjects [7.9%]; 4 events), however the number of events was similar.

In the Ximluci group, 1 ADA positive subjects (3.0%) had ophthalmic drug related TEAEs of moderate intensity in the study eye. In the Lucentis group, 1 ADA positive subject (2.6%) had drug-related ophthalmic TEAEs of moderate intensity in the study eye

Three cases of intravitreal signs of inflammation which could indicate immunoreaction were detected during the study duration of 52-weeks (two cases were reported in Lucentis and one in Ximluci treatment group).

In conclusion, the overall safety data does not indicate that Ximluci triggers immunogenicity reactions and causes safety related concerns in a larger extent than Lucentis, hence the data suggest that the immunogenicity profiles of the products are comparable. Furthermore, the safety profiles (including potential immunogenic events) for ADA-positive subjects treated with Ximluci are also comparable to the corresponding safety profile for Lucentis.

Table 31: Immunogenicity (Safety Set) (52 week data)

Visit	Variable Statistic	XSB-001 DP N=292	Lucentis N=289	Overall N=581
Baseline	NN	285	280	565
	Incidence of positive ADA, n (%)	12 (4.2)	8 (2.9)	20 (3.5)
	Titer, n (%)			
	<10	5 (1.8)	4 (1.4)	9 (1.6)
	10	0	0	0
	20	1 (0.4)	1 (0.4)	2 (0.4)
	40	2 (0.7)	3 (1.1)	5 (0.9)
	80	3 (1.1)	0	3 (0.5)
	160	0	0	0
	320	0	0	0
	640	1 (0.4)	0	1 (0.2)
	1280	0	0	0
	2560	0	0	0
	5120	0	0	0
	10240	0	0	0
	Incidence of NAb, n (%)	1/12 (8.3)	0	1/20 (5.0)
	Incidence of NAb, n (%)	1 (0.4)	0	1 (0.2)
Week 4	NN	273	272	545
	Incidence of positive ADA, n (%)	12 (4.4)	9 (3.3)	21 (3.9)
	Titer, n (%)			
	<10	3 (1.1)	4 (1.5)	7 (1.3)
	10	0	0	0
	20	4 (1.5)	2 (0.7)	6 (1.1)
	40	2 (0.7)	3 (1.1)	5 (0.9)
	80	1 (0.4)	0	1 (0.2)
	160	0	0	0
	320	1 (0.4)	0	1 (0.2)
	640	1 (0.4)	0	1 (0.2)
	1280	0	0	0
	2560	0	0	0
	5120	0	0	0
	10240	0	0	0
	Incidence of NAb, n (%)	0	0	0
	Incidence of NAb, n (%)	0	0	0
	Cumulative Incidence of positive ADA, n (%)	14 (4.8)	12 (4.2)	26 (4.5)

Week 8	NN	271	262	533
	Incidence of positive ADA, n (%)	7 (2.6)	6 (2.3)	13 (2.4)
	Titer, n (%)			
	<10	2 (0.7)	1 (0.4)	3 (0.6)
	10	0	0	0
	20	1 (0.4)	4 (1.5)	5 (0.9)
	40	2 (0.7)	1 (0.4)	3 (0.6)
	80	1 (0.4)	0	1 (0.2)
	160	1 (0.4)	0	1 (0.2)
	320	0	0	0
	640	0	0	0
	1280	0	0	0
	2560	0	0	0
	5120	0	0	0
	10240	0	0	0
	Incidence of NAb, n (%)	0	0	0
	Incidence of NAb, n (%)	0	0	0

Visit	**Variable Statistic**	**XSB-001 DP N=292**	**Lucentis N=289**	**Overall N=581**
	Cumulative Incidence of positive ADA, n (%)	14 (4.8)	14 (4.8)	28 (4.8)
Week 12	NN	265	258	523
	Incidence of positive ADA, n (%)	8 (3.0)	7 (2.7)	15 (2.9)
	Titer, n (%)			
	<10	1 (0.4)	3 (1.2)	4 (0.8)
	10	1 (0.4)	0	1 (0.2)
	20	1 (0.4)	1 (0.4)	2 (0.4)
	40	3 (1.1)	3 (1.2)	6 (1.1)
	80	0	0	0
	160	1 (0.4)	0	1 (0.2)
	320	0	0	0
	640	1 (0.4)	0	1 (0.2)
	1280	0	0	0
	2560	0	0	0
	5120	0	0	0
	10240	0	0	0
	Incidence of NAb, n (%)	1/8 (12.5)	0	1/15 (6.7)
	Incidence of NAb, n (%)	1 (0.4)	0	1 (0.2)
	Cumulative Incidence of positive ADA, n (%)	15 (5.1)	14 (4.8)	29 (5.0)

Week 20	NN	242	233	475
	Incidence of positive ADA, n (%)	15 (6.2)	9 (3.9)	24 (5.1)
	Titer, n (%)			
	<10	5 (2.1)	5 (2.1)	10 (2.1)
	10	0	0	0
	20	2 (0.8)	1 (0.4)	3 (0.6)
	40	4 (1.7)	1 (0.4)	5 (1.1)
	80	2 (0.8)	1 (0.4)	3 (0.6)
	160	1 (0.4)	0	1 (0.2)
	320	1 (0.4)	1 (0.4)	2 (0.4)
	640	0	0	0
	1280	0	0	0
	2560	0	0	0
	5120	0	0	0
	10240	0	0	0
	Incidence of NAb, n (%)	1/15 (6.7)	0	1/24 (4.2)
	Incidence of NAb, n (%)	1 (0.4)	0	1 (0.2)
	Cumulative Incidence of positive ADA, n (%)	22 (7.5)	15 (5.2)	37 (6.4)

Week 24	NN	248	251	499
	Incidence of positive ADA, n (%)	11 (4.4)	8 (3.2)	19 (3.8)
	Titer, n (%)			
	<10	2 (0.8)	4 (1.6)	6 (1.2)
	10	0	0	0
	20	2 (0.8)	1 (0.4)	3 (0.6)
	40	3 (1.2)	2 (0.8)	5 (1.0)
	80	1 (0.4)	1 (0.4)	2 (0.4)

Visit	Variable Statistic	XSB-001 DP N=292	Lucentis N=289	Overall N=581
	160	1 (0.4)	0	1 (0.2)
	320	0	0	0
	640	2 (0.8)	0	2 (0.4)
	1280	0	0	0
	2560	0	0	0
	5120	0	0	0
	10240	0	0	0
	Incidence of NAb, n (%)	0	0	0
	Incidence of NAb, n (%)	0	0	0
	Cumulative Incidence of positive ADA, n (%)	22 (7.5)	17 (5.9)	39 (6.7)
Week 36	NN	237	246	483
	Incidence of positive ADA, n (%)	15 (6.3)	16 (6.5)	31 (6.4)
	Titer, n (%)			
	<10	2 (0.8)	5 (2.0)	7 (1.4)
	10	1 (0.4)	2 (0.8)	3 (0.6)
	20	4 (1.7)	2 (0.8)	6 (1.2)
	40	3 (1.3)	2 (0.8)	5 (1.0)
	80	1 (0.4)	2 (0.8)	3 (0.6)
	160	1 (0.4)	1 (0.4)	2 (0.4)
	320	1 (0.4)	0	1 (0.2)
	640	1 (0.4)	0	1 (0.2)
	1280	1 (0.4)	0	1 (0.2)
	2560	0	1 (0.4)	1 (0.2)
	5120	0	0	0
	10240	0	1 (0.4)	1 (0.2)
	Incidence of NAb, n (%)	1/15 (6.7)	1/16 (6.3)	2/31 (6.5)
	Incidence of NAb, n (%)	1 (0.4)	1 (0.4)	2 (0.4)
	Cumulative Incidence of positive ADA, n (%)	29 (9.9)	25 (8.7)	54 (9.3)
Week 52	NN	231	226	457
	Incidence of positive ADA, n (%)	16 (6.9)	27 (11.9)	43 (9.4)
	Titer, n (%)			
	<10	2 (0.9)	11 (4.9)	13 (2.8)
	10	1 (0.4)	3 (1.3)	4 (0.9)
	20	4 (1.7)	4 (1.8)	8 (1.8)
	40	0	2 (0.9)	2 (0.4)
	80	2 (0.9)	2 (0.9)	4 (0.9)
	160	2 (0.9)	1 (0.4)	3 (0.7)
	320	1 (0.4)	1 (0.4)	2 (0.4)
	640	0	1 (0.4)	1 (0.2)
	1280	2 (0.9)	0	2 (0.4)
	2560	1 (0.4)	0	1 (0.2)
	5120	1 (0.4)	1 (0.4)	2 (0.4)
	10240	0	1 (0.4)	1 (0.2)
	Incidence of NAb, n (%)	4/16 (25.0)	6/27 (22.2)	10/43 (23.3)
	Incidence of NAb, n (%)	4 (1.7)	6 (2.7)	10 (2.2)

Visit	Variable Statistic	XSB-001 DP N=292	Lucentis N=289	Overall N=581
	Cumulative Incidence of positive ADA, n (%)	33 (11.3)	38 (13.1)	71 (12.2)

Abbreviations: ADA, anti-drug antibodies; Nab, neutralising antibodies; SS, safety set.
Note: Presented frequencies and the denominator used for percentages are based on subjects with relevant data at the visit (NN) in the SS and the actual treatment received group. For incidence of NAb within subjects with positive ADA, the denominator used for percentages is the number of subjects with a positive ADA result. For cumulative incidence of positive ADA, the presented frequencies are based on any data collected up to and including the visit and the denominator for percentages are based on all subjects in the SS.

2.4.8.5. Discontinuation due to adverse events

One subject (0.3%) in the XSB-001 DP (Ximluci) group and 2 subjects (0.7%) in the Lucentis group had an ophthalmic TEAE leading to withdrawal of study drug.

In the XSB-001 DP (Ximluci) group, 1 subject had a non-serious ophthalmic TEAE of moderate subretinal fluid in the study eye that led to withdrawal of study drug; the event was considered by the investigator to be related to study drug.
In the Lucentis group, 1 subject had a non-serious ophthalmic TEAE of moderate visual impairment in the study eye that led to withdrawal of study drug, which was considered by the investigator to be related to study drug. A second subject had a serious ophthalmic TEAE of severe endophthalmitis in the study eye that led to withdrawal of study drug, which was considered by the investigator to be related to study drug.

Two subjects (0.7%) in the Ximluci group and 5 subjects (1.7%) in the Lucentis group had non-ophthalmic TEAEs leading to withdrawal of study drug; none of these non-ophthalmic TEAEs were considered to be related to study drug.
In the Ximluci group, 2 subjects (0.7%) had non-ophthalmic TEAEs leading to withdrawal of study drug: 1 subject had serious TEAEs of anal cancer and vulval cancer, and 1 subject had a non-serious TEAE of pneumonia; these non-ophthalmic TEAEs were considered by the investigator to be not related to study drug.

In the Lucentis group, 5 subjects (1.7%) had non-ophthalmic TEAEs leading to withdrawal of study drug: 1 subject had a serious TEAE of oesophageal carcinoma, 1 subject had serious TEAEs of jaundice and pancreatic carcinoma, 1 subject had a non-serious TEAE of insomnia, 1 subject had serious TEAEs of bronchial carcinoma and lung adenocarcinoma, and 1 subject had serious TEAEs of atrial fibrillation and renal failure; these non-ophthalmic TEAEs were considered by the investigator to be not related to study drug.

The applicant has now provided the outstanding cumulative data on discontinuation rates from baseline to week 52

A total of 96 subjects (16.5%) discontinued the study treatment early, including 47 subjects (16.1%) in the Ximluci group and 49 subjects (16.9%) in the Lucentis group. The most common reason for early discontinuation of study treatment in both groups was subject request (ie, withdrawal of consent).

2.4.9. Discussion on clinical safety

The data relevant for comparability exercise in terms of safety comes from the Xplore study in patients with nAMD who were exposed to Ximluci and Lucentis.

Safety data up to 12 months has now been provided in the final CSR. Based on the currently available data, the safety data is considered supportive of clinical safety biosimilarity between Ximluci and Lucentis.

Overall, similar results were observed between the Ximluci group and the Lucentis group for safety assessments including laboratory tests, vital signs, slit lamp examinations, dilated fundus examinations, IOP measurements, colour fundus photography, and FA. A small increase in IOP (between 2 to 3 mmHg) was observed 30 minutes post-injection compared to pre-injection in both treatment groups.

The proportion of subjects who had at least 1 ophthalmic TEAE in the study eye was similar between the Ximluci group (105 subjects, 36.0%) and the Lucentis group (104 subjects, 36.0%). The majority of ophthalmic TEAEs in both treatment groups were mild in severity.

The proportion of subjects who had at least 1 ophthalmic TEAE in the study eye that was associated with an injection site reaction was similar between the Ximluci group (12.3%) and the Lucentis group (12.8%).

The proportion of subjects who had at least 1 ophthalmic study drug-related TEAE in the study eye was similar between the Ximluci group (22 subjects [7.5%]; 29 events) and the Lucentis group (28 subjects [9.7%]; 41 events). Conjunctival haemorrhage, retinal pigment epithelial tear, and injection site pain were the most commonly reported ophthalmic study drug-related TEAEs.

The Applicant was asked to further discuss the topic of subretinal fluid. Twice as many patients were reported as having subretinal fluid in the Ximluci group (n=6, 2.1%) compared with n=3 (1.0%) for Lucentis. 1 of the subjects in the Ximluci group had a non-serious ophthalmic TEAE of moderate subretinal fluid in the study eye that led to withdrawal of study drug; the event was considered by the investigator to be related to study drug. This is not a listed ADR for Lucentis, although 'retinal disorders' are generally included. The applicant has provided a detailed discussion in their responses acknowledging that 6 out of 292 (2.1%) in the Ximluci group and 3 out of 289 (1.0%) patients in the Lucentis-group were reported as having AE sub-retinal fluid in the study eye. Given the equivalence demonstrated at the primary, Week 8 timepoint, high degree of similarity demonstrated on sensitive anatomical endpoints, pharmacokinetic data as well as the similarity demonstrated in the comprehensive comparative analytical assessment package between Ximluci and Lucentis, there is no basis to believe that a difference in retinal disorders or sub-retinal fluid specifically is plausible. This is considered acceptable.

Two subjects in each treatment group had a non-ophthalmic study drug-related TEAE.

The proportion of subjects who had at least 1 non-ophthalmic TEAE was slightly higher in the Lucentis group (52.9%) compared to the Ximluci group (45.9%). The majority of non-ophthalmic TEAEs in both treatment groups were mild or moderate in severity.

In the Ximluci treatment group, an event of mild myocardial ischaemia was reported (assessed as non-serious), while an event of severe myocardial infarction was reported in the Lucentis treatment group (assessed as serious). Regarding the event of mild myocardial ischaemia, the applicant has provided further information about this event. Following assessment of the Applicant's response, it is concluded that this does not comply with any of the severity criteria to be considered a serious adverse event given that this event did not lead the patient to hospitalization, did not require extensive procedural or an extensive drug treatment, and was not life-threatening. The dose of the study drug was not changed either.

A total of 11 subjects died during the study (8 subjects in the Ximluci group and 3 subjects in the Lucentis group); none of the deaths were considered related to study drug by the investigator.
In the Ximluci group, 1 subject died due to cardiopulmonary failure 1 subject died due to COVID-19; 1 subject died of unknown cause, 1 subject died of acute renal failure, 1 subject died of cardiac arrest, 1 subject died of chest pain and COVID-19 , 1 subject died of presumed congestive heart failure; the subject had SAEs of urinary tract infection and arthralgia, which were considered by the investigator to

be not related to study drug and had an outcome of fatal. 1 subject was reported to have died of death (biological death).

In the Lucentis group, 1 subject died due to acute pancreatitis, 1 subject died due to acute pancreatitis and myocardial infarction, 1 subject died due to COVID-19. As for the interim analysis, none of the deaths were considered by the investigator to be related to the study drug in any treatment group. However, it is noted that there was a trend towards a slightly higher number of fatal reports for Ximluci compared with Lucentis over the 52-week treatment period. The Applicant states that the fatal cases reported during the pivotal clinical trial were not considered related to treatment by the investigator. In view of the fact that biosimilarity has generally been shown for this product, the imbalance in fatal cases noted in the Ximluci treatment group is unlikely to be related to the study treatment. Nevertheless, for a small number of fatal cases reported in the Ximluci treatment group, sufficient information was initially not submitted. For completeness, the Applicant was requested to further discuss the reported imbalance in fatal cases for the Ximluci treatment group and to present any further information relating to these cases which may have become available. The applicant has provided all available details on the fatal cases noted in the Ximluci treatment group and has discussed the slight numerical imbalance in fatal cases is noted. The applicant has outlined that one possible explanation for the slight imbalance in the number of fatalities in the Ximluci vs. Lucentis group is that the Ximluci group is represented by slightly older subjects. A total of 11 subjects died during the study (8 subjects in the Ximluci group and 3 subjects in the Lucentis group); none of the deaths were considered related to study drug. In view of the fact that biosimilarity has generally been shown for this product and no difference in safety profiles has been shown, this slight numerical imbalance in fatal cases noted in the Ximluci treatment group is unlikely to be related to the study treatment.

Ophthalmic, serious TEAEs were reported in 4 subjects (1.4%) in the Ximluci group and 4 subjects (1.4%) in the Lucentis group.

Non-ophthalmic serious TEAEs were reported in 28 subjects (9.6%) in the Ximluci group and 31 subjects (10.7%) in the Lucentis group.

According to Xplore study protocol, treatment-emergent adverse events (TEAE) were defined as AEs that began or worsened in severity after the IVT injection of the study drug; while an AE was defined as an event that occur after a patient provides informed consent but before the time of the first dose of study drug.

The event of "hip fracture" for a patient was considered a SAE, but not a serious TEAE. Reviewing the narrative of this event, the patient experienced the adverse event after the first IVT injection of the study drug (Ximluci). The Applicant was invited to explain why this event was not considered a serious TEAE if, according to the definition, this event happened after the first dose of the study drug was administered. The applicant has provided a detailed response. It is concluded that the narrative of the event is somewhat unclear given that it is said that the event happened after the first injection of the treatment (definition of a TEAE) and later it says that it happened on an unkown date, which is considered the correct to have recorded the onset date as "unknown date" if the date was not provided. Either way, this explanation is acknowledged and no further explanation is required.

In the listed SAEs presented in the table 2.5: 9, regarding "Respiratory, thoracic and mediastinal disorders" events, there are 2 events in total (happened in 2 subjects) in the Lucentis group, but only 1 event (happened in 1 subject) of dyspnoea is listed.

In the next table (2.5: 10), regarding "Respiratory, thoracic and mediastinal disorders" events, is listed also and event of "pulmonary oedema" (in addition to the event of "dyspnoea") in the Lucentis group. They are counted 2 events in total, which is right. This event might be missing from the previous table.

The applicant has now provided an amended table and has included all the data for the 52 weeks of treatment. This data has been reviewed and it is correct.

One subject (0.3%) in the Ximluci group and 2 subjects (0.7%) in the Lucentis group had an ophthalmic TEAE leading to withdrawal of study drug. In the Ximluci group, 1 subject had a non-serious ophthalmic TEAE of moderate subretinal fluid in the study eye that led to withdrawal of study drug; the event was considered by the investigator to be related to study drug.

In the Lucentis group, 1 subject had a non-serious ophthalmic TEAE of moderate visual impairment in the study eye that led to withdrawal of study drug, which was considered by the investigator to be related to study drug. A second subject had a serious ophthalmic TEAE of severe endophthalmitis in the study eye that led to withdrawal of study drug, which was considered by the investigator to be related to study drug.

In the Ximluci group, 2 subjects (0.7%) had non-ophthalmic TEAEs leading to withdrawal of study drug: 1 subject had serious TEAEs of anal cancer and vulval cancer, and 1 subject had a non-serious TEAE of pneumonia; these non-ophthalmic TEAEs were considered by the investigator to be not related to study drug.

In the Lucentis group, 5 subjects (1.7%) had non-ophthalmic TEAEs leading to withdrawal of study drug: 1 subject had a serious TEAE of oesophageal carcinoma, 1 subject had serious

TEAEs of jaundice and pancreatic carcinoma, 1 subject had a non-serious TEAE of insomnia,

1 subject had serious TEAEs of bronchial carcinoma and lung adenocarcinoma, and 1 subject had serious TEAEs of atrial fibrillation and renal failure; these non-ophthalmic TEAEs were considered by the investigator to be not related to study drug.

The results for laboratory tests, vital signs, slit lamp examinations, dilated fundus examinations, IOP measurements, colour fundus photography, and FA were similar between the XSB-001 DP (Ximluci) group and the Lucentis group.

Immunogenicity

To compare the immunogenicity between XSB-001 DP (Ximluci) and Lucentis, blood samples were collected for evaluation of anti-drug antibody (ADA) and neutralising anti-drug antibody (NAb) at baseline and at various times throughout the study period (Day 0, Weeks 4, 8, 12, 20, 24, 36, and 52) from all patients on the Clinical Phase 3 study. Additional samples for immunogenicity testing were collected from patients with any sign of intraocular inflammation as they may indicate an immune reaction.

The full 52-week immunogenicity data has now been submitted.

In the study drug group, there were 1 sample Nab positive at baseline, at week 12 and at week 20 versus none in the Lucentis group (table 2.5:13).

At baseline, the incidence of positive ADA was 12 subjects (4.2%) in the Ximluci group and 8 subjects (2.8%) in the Lucentis group. Between baseline and week 12, there were no notable differences in immunogenicity results between the Ximluci and Lucentis groups and the incidence of positive ADA was similar between treatment groups. At Week 24, the cumulative incidence of positive ADA was 7.5% in the Ximluci group and 5.9% in the Lucentis group. It was noted that there is a numerically higher incidence of positive ADAs in the Ximluci group at week 24 when compared to the Lucentis arm.

The applicant has since provided the outstanding immunogenicity data for both treatment groups from week 24 onwards and from this additional data there appears to be no notable differences in

immunogenicity results between the XSB-001 DP and Lucentis groups over time. The potential for immunogenicity was observed to be low in the general Xplore study population. The incidence of positive results was low (≤ 7.5% of patients at any visit in the XSB- 001 DP (Ximluci) group compared with ≤11.9% in the Lucentis group).

At Week 52, the cumulative incidence of positive ADA was 33 subjects (11.3%) in the XSB-001 DP (Ximluci) group and 38 subjects (13.1%) in the Lucentis group.

In conclusion, the overall safety data does not indicate that Ximluci triggers immunogenicity reactions and causes safety related concerns in a larger extent than Lucentis, hence the data suggest that the immunogenicity profiles of the products are comparable. Furthermore, the safety profiles (including potential immunogenic events) for ADA-positive subjects treated with Ximluci are also comparable to the corresponding safety profile for Lucentis.

The mean overall ranibizumab exposure was 5.78 mg in the Ximluci group and 5.80 mg in the Lucentis group.

The mean ranibizumab treatment duration was 311.9 days in the XSB-001 DP group and 312.3 days in the Lucentis group. A total of 184 subjects (63.0%) in the Ximluci group and 178 subjects (61.6%) in the Lucentis group received all 13 doses of ranibizumab over the study.

At Week 52, there is a similar trend in reporting adverse events in comparison with the data provided at Week 24. The overall safety profile from the available data as reflected by the most frequently reported TEAEs, severity of the TEAEs and number reported as related, is generally consistent with the known safety profile of Lucentis. The intensity of the TEAEs reported remains mild.

It can be concluded that the safety of Ximluci was expected according to the already known safety information of Lucentis, and it is in line with its SmPC.

2.4.10. Conclusions on the clinical safety

The full 52-week safety data from the pivotal clinical trial has been provided. The overall safety profile can be considered similar to that which is already established for Lucentis. From a safety perspective, no notable differences in the safety risks have been identified between Ximluci and Lucentis from the 52-week data provided with the application.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of 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.

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infectious endophthalmitis	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 6.6* Additional risk minimisation measures: *Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of infectious endophthalmitis and when to seek urgent attention from the physician.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Targeted follow-up using targeted checklist.* Additional pharmacovigilance activities: *None*
Intraocular inflammation	Routine risk minimisation measures: *SmPC sections 4.3 and 4.4* Additional risk minimisation measures: *Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of intraocular inflammation and when to seek urgent attention from the physician.*	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* Additional risk minimisation measures: *Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	signs and symptoms of retinal detachment and retinal tear and when to seek urgent attention from the physician.	
Intraocular pressure increase	Routine risk minimisation measures: *SmPC sections 4.4, 4.8 and 4.9* Additional risk minimisation measures: *Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of IOP and when to seek urgent attention from the physician.*	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 0.3 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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: No full user consultation with target patient groups on the package leaflet has been performed on the

basis of a bridging report making reference to Lucentis. The bridging report submitted by the applicant has been found acceptable.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Ximluci has been developed as a biosimilar ranibizumab using Lucentis as a reference product and is intended to be used in the same adult indications as the EU approved reference product Lucentis.

A comprehensive **analytical similarity** study was performed by the Applicant for the purpose of demonstration of biosimilarity at the quality level. The biosimilarity exercise included a side-by-side comparative analytical assessment (batches of EU Lucentis, batches of US Lucentis and batches of XSB-001) and stability studies to compare degradation profiles. The applicant's approach for demonstrating biosimilarity is aligned with the relevant EMA guidelines and thus considered acceptable. The selection of batches and assignment of criticality of quality attributes (QAs) for the comparative assessment is presented in a clear logical manner and is considered acceptable.

A large panel of methods has been used to characterise and compare the most relevant physicochemical and biological quality attributes of the ranibizumab molecule.

The **non-clinical programme** included several *in vitro* pharmacodynamic studies. Binding of XSB-001, EU Lucentis and US Lucentis to VEGF-A was assessed by surface plasmon resonance measurements. Comparability assessment of bioactivity was by means of a reporter gene assay involving KDR/NFAT-RE HEK293 cells. The suitability of the reporter gene assay was verified by using a HUVEC proliferation assay. Four different isoforms of VEGF-A were included in the studies and most weight was given to the results for the predominant isoform 165. In general, binding and bioactivity of XSB-001 (Ximluci) were within the defined comparative assessment ranges for the reference products, suggesting similarity. A GLP-compliant, single dose comparative study was also conducted to evaluate the PK and toxicity profiles of XSB-001 (Ximluci) and Lucentis. The results of this study did not identify any significant differences between XSB-001 (Ximluci) and the RMP from a nonclinical perspective.

The **clinical development** consisted of one main clinical study a multicentre, double-masked, randomised, parallel group, phase 3 study (Study Xplore comparing efficacy, safety, immunogenicity, and pharmacokinetics (PK) of XSB-001 DP (Ximluci), (also known as Xlucane during development) to that of the reference product Lucentis, in patients with newly diagnosed neovascular age-related macular degeneration (wAMD).

3.2. Results supporting biosimilarity

At the quality level, the results of the comparative analytical assessment demonstrated that the primary and higher order structure, functionally binding and bioactivity to four isoforms of VEGF A of XSB-001 DP (Ximluci) is highly comparable to EU Lucentis and US Lucentis. For purity and related species, some minor differences were observed in XSB-001 (Ximluci) batches, however, are not considered to have any meaningful impact, hence do not impact on the biosimilarity claim. In summary, at the quality level while data presented could support similarity between XSB-001 (Ximluci) and both EU and US Lucentis.

Similarly, the non-clinical programme supports biosimilarity in terms of binding and bioactivity.

As the main clinical study, the Applicant submitted one randomised controlled study (Xplore) with Lucentis as an active comparator in patients with neovascular age related macular degeneration to

support the claim for similarity. The study is an equivalence study with equivalence boundaries of ± 3.5 letters BCVA.

In terms of efficacy, the primary endpoint of change from baseline in BCVA was assessed at Week 8 (in line with scientific advice) when the gain in BCVA for Ximluci was 4.6 letters (95% CI from 3.5 to 5.6 letters). The gain for Lucentis was 6.4 letters (95% CI from 5.3 to 7.4 letters). The LS mean difference in change from baseline BCVA between the two treatment arms at Week 8 was – 1.8 letters with 95% CI from -3.1 to -0.4 letters. As the 95% CI were within the margins of ± 3.5 letters it can be concluded that equivalence has been demonstrated at Week 8. Furthermore, Ximluci and Lucentis demonstrate a high degree of similarity of treatment effects on sensitive anatomical endpoints including CFT, total size of CNV leakage area, number of intraretinal cysts, amount of sub-retinal fluid and size of retinal PEDs.

A total of 40 subjects in the Ximluci group and 30 subjects in the Lucentis group were included in the PK sub-study. The plasma ranibizumab concentrations were similar between the Xlucane and Lucentis groups at Day 1 and Week 20.
The data relevant for comparability exercise in terms of safety comes from the same study. Only data from the interim safety analysis at week 24 was provided with the initial submission. However, the outstanding safety data up to week 52 has been provided during the procedure. Following review of this 52-week data, the overall safety profile as reflected by the most frequently reported TEAEs, severity of the TEAEs and number reported as related, is generally consistent with the known safety profile of Lucentis and in line with safety characteristics reported in the Lucentis labelling/SmPC.

It had been noted that there is a numerically higher incidence of positive ADAs in the Ximluci group at week 24 when compared to the Lucentis arm. During the evaluation, the applicant has provided a detailed overview and discussion on the immunogenicity data for both treatment groups up to 52 weeks. From this additional data there appears to be no notable differences in immunogenicity results between the XSB-001 DP and Lucentis groups over time. The potential for immunogenicity was observed to be low in the general Xplore study population. The incidence of positive results was low (≤ 7.5% of patients at any visit in the XSB- 001 DP (Ximluci) group compared with ≤11.9% in the Lucentis group).

At Week 52, the cumulative incidence of positive ADA was 33 subjects (11.3%) in the XSB-001 DP (Ximluci) group and 38 subjects (13.1%) in the Lucentis group. The correlation of ADAs to AEs has been reported for each treatment group also.

In conclusion, the overall safety data does not indicate that Ximluci triggers immunogenicity reactions, nor causes safety related concerns in a larger extent than Lucentis, hence the currently available data indicates that the immunogenicity profiles of the products are comparable. Furthermore, the safety profiles (including potential immunogenic events) for ADA-positive subjects treated with Ximluci are also comparable to the corresponding safety profile for Lucentis.

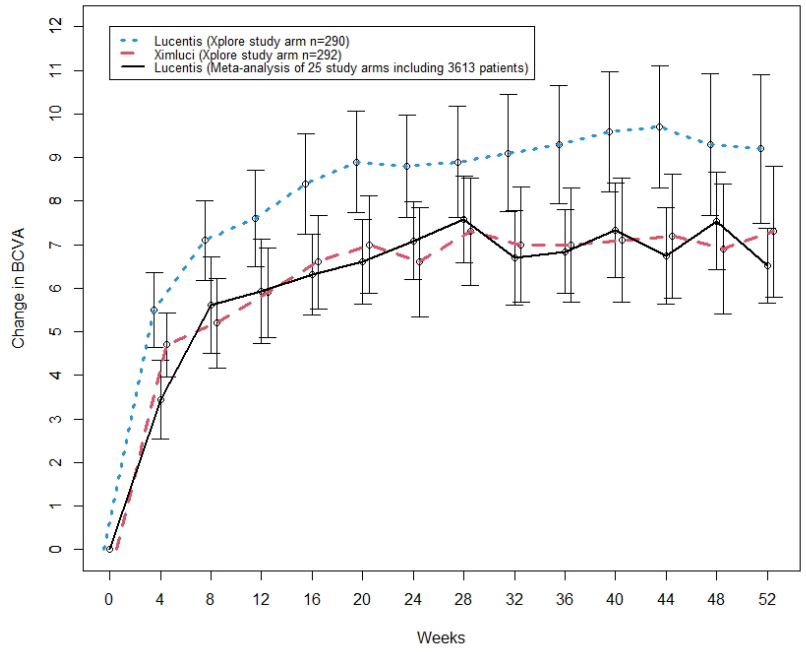
3.3. Uncertainties and limitations about biosimilarity

There were uncertainties with regard to the maintenance of similarity throughout the treatment period. An increase in the difference in change from baseline BCVA between the two treatment arms was seen at Week 20 and particularly at Week 24. At Week 24 the LS mean for change from baseline in BCVA was 5.8 for Ximluci and 8.1 for Lucentis. The LS mean difference was -2.3 with 95% CI -4.0 to -0.6. Further data was provided by the Applicant which showed that reduction in BCVA was greater for Lucentis than Ximluci at all 4 weekly time points between Week 28 to Week 52 inclusive. However, the differences in BCVA observed at Week 24 (-2.27 [95% CI -3.93 to -0.61]) were reduced at Week 52 (-1.46 [95% CI -3.62 to 0.69]). The Applicant also argued that the results for Ximluci are similar to the results shown in a meta-analysis of randomised controlled ranibizumab studies including over 3500 patients from 22 clinical studiesand that in comparison to historical performance, Lucentis over performed in the Xplore

study (Figure 5). In addition, in terms of change from baseline in sensitive anatomical endpoints such as CFT, total size of CNV leakage area, number of intraretinal cysts, amount of sub-retinal fluid and size of retinal PEDs, Ximluci showed comparability over the whole 52-week treatment period. These anatomical endpoints are considered sensitive outcome measures and some of them have been accepted as primary endpoint in previous MAs. The data did not show any directional consistency of the effect on anatomical endpoints favouring Lucentis.

Overall, the uncertainties are considered resolved.

Figure 5: Meta-analysis of the effect of ranibizumab on improvement in BCVA, adjusted for baseline BCVA, for wAMD patients. Estimated improvement (dots) and 95% confidence intervals (bars) are calculated based on a random effects model from 22 studies and 3613 patients. Mean change from baseline for Ximluci (Xlucane) and Lucentis based on the Xplore study are plotted in red and blue alongside both bar-plots



3.4. Discussion on biosimilarity

Ximluci and Lucentis were judged to be highly similar at the quality level and at Ximluci met its primary endpoint at Week 8, a time-point that is likely to be the most sensitive to differences in efficacy between the treatment arms.

Also in light of the assessment of the full 52-week dataset submitted during the application, and of the satisfactory manner the uncertainties mentioned above were addressed, biosimilarity can be considered demonstrated.

3.5. Extrapolation of safety and efficacy

Data on clinical comparability has been provided in one indication, that is, in Patients with Neovascular Age-Related Macular Degeneration. Considering that the protein structure for Ximluci is identical to ranibizumab, and in vitro binding to VEGF-A receptor isoforms and functional bioactivity were

comparable from a non-clinical perspective, safety and efficacy can be extrapolated to all the indications applied for.

3.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ximluci 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 Ximluci is favourable in the following indication(s):

Ximluci 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.