EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2025
EMA/CHMP/272837/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eyluxvi

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006282/0000

Note

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

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List of abbreviations

2-AB	2-Aminobenzamide acid
ADA	Anti-Drug Antibodies
ADR	Adverse Drug Reaction
AE	Adverse Event
AEX	Anion Exchange Chromatography
AMD	Age-related Macular Degeneration
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
BCVA	Best-Corrected Visual Acuity
BWP	Biologics Working Party
C	Concentration
CCF	Cell Culture Fluid
CCS	Container Closure System
CD	Circular Dichroism
CE-SDS	Capillary Electrophoresis Sodium Dodecyl Sulphate
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
cGMP	Current Good Manufacturing Practice
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
cIEF	Capillary Isoelectric Focusing
CIPC	Critical In-process Controls
CNV	Choroidal Neovascularisation
CPP	Critical Process Parameters
DME	Diabetic Macular Oedema
DP	Drug Product
DR	Diabetic Retinopathy
DS	Drug Substance
ECL	Electrochemiluminescence
ELISA	Enzyme-linked Immunosorbent Assay
EP	European Pharmacopoeia
ERA	Environmental Risk Assessment

ERP	Enterprise Resource Planning
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	Endotoxin Unit
EU	European Union
FDA	Food and Drug Administration
Flt-1	Fms related receptor tyrosine kinase 1
FT-IR	Fourier Transform-Infrared Spectroscopy
GC/MS	Gas Chromatography/Mass Spectrometry
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCCF	Harvested Cell Culture Fluid
HCD	Host Cell DNA
HCP	Host Cell Protein
HI-HPLC	Hydrophobic Interaction-High Performance Liquid Chromatography
HILIC-UPLC	Hydrophilic Interaction-Ultra Performance Liquid Chromatography
HMW	High Molecular Weight
HUVEC	Human Umbilical Vein Endothelial Cells
ICH	The International Conference on Harmonisation of Technical Requirements for Pharmaceutical for Human Use
ICS	Ion Chromatography
IEF	Isoelectric Focusing
IGF-1	Insulin like Growth Factor 1
IgG1	Immunoglobulin gamma 1
INN	International Non-proprietary Name
IPC	In-process control
IPM	In-process monitoring
IPS	In-process specification
IRS	Interim Reference Standard
IVT	Intravitreal
JP	Japanese Pharmacopoeia
kDa	Kilo Dalton
KDR	Kinase Insert Domain Receptor
KPP	Key Process Parameters

LC-ESI-MS/MS	Liquid Chromatography Electrospray Ionisation and Tandem Mass Spectrometry
LC-ESI-Q-TOF MS	Liquid Chromatography-Electrospray Ionisation tandem-Quadrupole Time of Flight-Mass Spectrometry
LC-MS	Liquid Chromatography and Mass Spectrometry
LMW	Low Molecular Weight
LoQ	Limit of Quantification
MAA	Marketing Authorisation Application
MALDI-TOF	Matrix-Assisted Laser Desorption Ionisation-Time of Flight
MCB	Master Cell Bank
MEM	Minimum Essential Medium
MMC	Multi Modal Anion Exchange Chromatography
MSX	L-Methionine Sulfoximine
MVM	Minute Virus Mouse
MW	Molecular Weight
N/A	Not Applicable
N/D	Not Detected
NKPP	Non-key Process Parameter
PDE	Permitted Daily Exposure
Ph.Eur.	European Pharmacopoeia
pI	Isoelectric Point
PlGF	Placental Growth Factor
PK	Pharmacokinetics
PPCB	Post Production Cell Bank
PPQ	Process Performance Qualification
PRS	Primary Reference Standard
QC	Quality Control
Q-TOF	Quadrupole Time-of-Flight
RCB	Research Cell Bank
RefMP	Reference Medicinal Product
ROP	Retinopathy of Prematurity
SEC-MALS	Size Exclusion Chromatography-Multi-Angle Light Scattering
SE-HPLC	Size Exclusion-High Performance Liquid Chromatography
SV-AUC	Sedimentation Velocity Analytical Ultracentrifugation

TFF	Tangential Flow Filtration
TK	Toxicokinetics
TSE	Transmissible Spongiform Encephalopathy
UPLC	Ultra-Performance Liquid Chromatography
UPLC-FLD	Ultra Performance Liquid Chromatography-Fluorescence Detection
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WCB	Working Cell Bank
WHO	World Health Organization
WRS	Working Reference Standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biolitec Pharma Limited Zweigniederlassung Jena submitted on 29 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Eyluxvi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 January 2023.

The applicant applied for the following indication:

Eyluxvi is indicated for adults for the treatment of

- *neovascular (wet) age-related macular degeneration (AMD) (see section 5.1)*
- *visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1)*
- *visual impairment due to diabetic macular oedema (DME) (see section 5.1)*
- *visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).*

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: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/12/797/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/12/797/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number(s): EU/1/12/797/001-002

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
16 September 2021	EMA/SA/0000063713	Silvijus Abramavicius, Linda Trauffler

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

- Overall biosimilarity programme, comparative stability programme, specifications.
- Adequacy of the performed in vivo non-clinical studies.
- Design of a Phase III efficacy, safety, tolerability, immunogenicity, and PK comparability study: overall design, patient population, primary and secondary endpoints, timing of samples, dosage, masking, source of the reference medicinal product, sample size, statistical methods for data analysis; extrapolation of clinical study data to all approved indications of the reference medicinal product.

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: Antonio Gomez-Outes

The application was received by the EMA on	29 June 2024
The procedure started on	18 July 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	7 October 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	21 October 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	14 November 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 April 2025
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	16 April 2025
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 Eyluxvi on	24 July 2025

2. Scientific discussion

2.1. About the product

Eyluxvi 40 mg/mL solution for injection in a vial has been developed as a biosimilar to the reference product Eylea (INN: aflibercept) 40 mg/ml solution for injection.

Aflibercept is in the pharmaceutical group ophthalmologicals, antineovascularisation agents (ATC code: S01LA05).

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human immunoglobulin G1. It acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors and thereby can inhibit the binding and activation of these cognate VEGF receptors.

The claimed therapeutic indications for Eyluxvi are in adults for treatment of

- neovascular (wet) age-related macular degeneration (AMD),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO),
- visual impairment due to diabetic macular oedema (DME),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV).

The paediatric indication of treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease in preterm infants – granted to Eylea 40 mg/mL solution for injection in pre-filled syringe - is not claimed for Eyluxvi.

2.2. Quality aspects

2.2.1. Introduction

This medicinal product has been developed as a biosimilar to the EU reference medicinal product (RefMP) Eylea (EMEA/H/C/2392). It contains the active substance aflibercept (also referred to as ALT-L9), a fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

The finished product is presented as a solution for intravitreal injection in a single-use vial where aflibercept is formulated with L-histidine, sucrose, polysorbate 20, hydrochloric acid and water for injections.

One vial contains an extractable volume of at least 0.1 mL, equivalent to at least 4 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept. The vial is co-packaged with a filter needle.

2.2.2. Active Substance

General Information

ALT-L9 (aflibercept) is a highly purified 864 amino acid (2 × 432 amino acids) recombinant protein consisting of sequences derived from domain 2 of human VEGFR-1 (also known as Flt-1), domain 3 of VEGFR-2 (also known as KDR or Flk-1) and the Fc portion of human IgG1. It is a homodimeric glycoprotein connected through two intermolecular disulfide bonds.

The de-glycosylated intact mass profile is approximately 97 kDa. The most abundant species among the glycosylated intact mass profile is approximately 112 kDa due to N-glycosylation on each monomer.

ALT-L9 has been designed to attach to and block the effects of a substance called vascular endothelial growth factor A (VEGF-A). It can also attach to other proteins such as placental growth factor (PlGF). VEGFA and PlGF are involved in stimulating the abnormal growth of blood vessels in patients with age-related macular degeneration, certain types of macular oedema, myopic choroidal neovascularisation and retinopathy of prematurity. By blocking these factors, aflibercept reduces the growth of abnormal blood vessels and controls leakage and swelling.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substrate manufacturing site is responsible for the active substance manufacturing, in-process and quality control release testing. All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

ALT-L9 is produced in CHO-K1 cells.

Briefly, one vial of working cell bank (WCB) is expanded in several steps in shake flasks and bioreactor. The bioreactor is harvested and clarified, and subsequently the active substance is purified

by chromatography steps. Virus clearance steps are performed and pools concentrated and diluted to the final protein concentration. After filtration, the active substance is stored frozen.

No reprocessing is claimed.

Control of Materials

Raw materials are generally described in sufficient detail. The applicant has provided a risk assessment regarding extractables and leachables addressing all product contact materials used in manufacturing process.

The source, history, and generation of the cell substrate and generation, characterisation and testing of the cell bank system is described in line with ICH Q5B and ICH Q5D. A two-tiered cell bank has been established in which the master cell bank (MCB) which is used to generate WCBs. The applicant has presented the protocol for future WCBs.

Control of Critical Steps and Intermediates

In general, there are sufficient controls on the process in terms of parameters and in process tests. Controls have been developed in line with process development and risk management principles of ICH Q9 and Q11 The categorisation of criticality of parameters and controls is based on risk assessments which are presented in S.2.6. Clear definitions are presented what constitutes a critical process parameter (CPP), key or non-key process parameter (KPP, NKPP), in-process control (IPC) and critical IPC and in-process monitoring (IPM). The action when limits or specifications are exceeded for each category are described. The applicant has provided a description and qualification of the analytical methods that are used as IPCs.

Process validation

Process validation activities included process consistency / process performance qualification (PPQ), shipping studies, impurity clearance studies, viral clearance studies, process intermediate hold studies, column and membrane lifetime studies and a supporting active substance dispensing qualification study.

Following the completion of PPQ studies, process parameters and in-process test were reevaluated, and several modifications were made to the process control strategy and process parameter classification driven by additional manufacturing and process development experience obtained during the PPQ campaign. Performance of shipping from the active substance manufacturing site to the finished product manufacturing site was qualified.

Impurity clearance has been validated for cell derived impurities, cell culture process derived impurities, and impurities derived from the purification process.

Process intermediate holds have been validated. Information on the impact of the hold times on the microbiological quality of the process intermediates has been provided.

Column cycling studies have been performed at laboratory scale to determine resin lifetime. Data to support the proposed membrane cycles for the TFF membranes is provided along with information on the current total number of cycles used for columns and membranes that were confirmed at manufacturing scale.

Manufacturing process development

The history of batch manufacture usage and development is presented.

An iterative process of risk assessment has been conducted throughout development on the product and process to determine the criticality of product quality attributes and identify, characterise, mitigate and control high and moderate risk process parameters.

In general, the approach to process development is considered comprehensive and all relevant data is presented in the dossier.

Extensive comparability has been conducted to demonstrate the comparability of the product during development in line with ICH Q5E. Comparability studies have addressed each iteration of the process described in manufacturing process development, and each process has been demonstrated to be comparable to the next iteration. Overall, the approach to setting comparability acceptance criteria is acceptable and it is agreed the different versions of the process are comparable.

Characterisation

A comprehensive extended characterisation study has been presented to confirm the structure and physicochemical characteristics of the active substance and finished product.

The characterisation data are consistent between the active substance batches and finished product batches The approach is considered in general to be in accordance with the Guideline on development, production, characterisation and specification for monoclonal antibodies and related products (EMA/CHMP/BWP/532517/2008), ICH Q6B and general Ph. Eur. monographs 0784.

Process-related impurities and product-related impurities are identified. The applicant has provided summaries of the toxicological assessment for certain process related impurities/chemical compounds to justify the safety limits stated.

A nitrosamine impurity risk assessment for ALT-L9 has been conducted and concludes that there is no risk from the active substance, its manufacturing process, formulation and packing materials.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The ALT-L9 specifications are generally appropriate and address general properties, identity, quantity, purity, potency and safety related testing (bacterial endotoxins, microbiological purity) which is in line with ICH Q6B and is considered appropriate for routine control of a monoclonal antibody at release.

Analytical procedures

Compendial analytical procedures include colour, clarity, osmolality, pH, bacterial endotoxins and bioburden and are performed in accordance with the Ph. Eur. The non-compendial methods proposed were described.

Verification has been performed for the compendial methods. The analytical procedures have been appropriately validated in accordance with ICH Q2(R1). For the non-compendial methods, summaries of the validations have been submitted for each assay.

Batch analysis

Batch analysis data is provided. The data demonstrate that the commercial process is capable of manufacturing a consistent active substance.

The specifications have been based on commercial acceptance criteria from batch analysis data of commercial scale active substance batches and are accepted.

Reference Standards

A two-tier reference standard system has been established in line with ICH Q6B and ICH Q7. Establishment of the primary reference standard (PRS) and working reference standard (WRS) are described along with information on previous reference standards.

Container Closure

The container closure system is a Biotainer bottle with an screw cap. Compatibility studies have been presented. Extractable and leachable studies provided have shown that no compounds of concern have been detected.

Stability

The shelf-life for ALT-L9 active substance when stored at recommended long-term storage temperature in the container closure system described in Section 3.2.S.6 Container Closure System is proposed.

Primary stability studies have been conducted in line with relevant stability guidance ICH Q5C and ICH Q1A (R2).

The applicant has confirmed that any changes made to the analytical methods throughout development were minor and had no impact on the results obtained from the method.

The data provided supports the proposed shelf-life for the active substance when stored at long-term storage condition.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

ALT-L9 finished product has been developed as an intended biosimilar of Eylea. ALT-L9 finished product is a clear and colourless to pale yellow solution in a glass vial, for intravitreal use. One single-use vial contains aflibercept as the active substance.

All excipients are Ph. Eur. grade, and the choice and concentration of the excipients were determined in experiments described in section P.2.2. There are no materials of animal or human origin listed in the finished product composition. No novel excipients are identified.

The vial containing the finished product is co-packaged with filter needle intended to withdraw the vial content.

Pharmaceutical development

The quality target product profile (QTPP) was established based on the Ref MP Eylea and the CQAs of the finished product have been established based on a risk assessment discussed in section S.2.6.

There are no overages. The administered dose is 0.05 mL to the eye, hence, the overfill is deemed sufficient to allow withdrawal of the minimum dosage of 0.05 mL.

ALT-L9 has had three different finished product manufacturing processes throughout its development.

The changes made throughout the different development stages have been highlighted along with a classification of the changes impact on process quality and process performance. The changes are mostly considered as minor and are due to the increase in scale between the processes.

After identification of the CQAs a process risk assessment was performed to identify the process parameters which impacted CQAs and process performance.

A number of parameters were not evaluated in any process characterisation studies but were operated at worst case scenario for the PPQ validation.

A second risk assessment was performed following the process characterisation studies. The current ranking of CPPs, KPPs and NKPPs is deemed acceptable.

Following the completion of the PPQ, parameter limits were reviewed, and a number of the parameters were changed. As all the changes were to include tighter control over the parameter this is deemed acceptable.

Overall, the changes throughout the manufacturing process have been adequately described. An acceptable approach for demonstrating comparability between the different processes used to produce the finished product has been presented in S.2.6.

Manufacture of the product and process controls

All sites involved in manufacture and control of the finished product operate in accordance with EU GMP.

The ALT-L9 is formulated with the listed excipients during the active substance manufacturing process and then during the finished product manufacturing process. The applicant has provided a batch formula and quantity of excipients per batch.

The vial finished product manufacturing process is relatively straightforward as the product is fully formulated during active substance manufacturing. The finished product process begins with the active substance being thawed. The ALT-L9 is then filtered. The finished product is concurrently filled aseptically. Following filling, the vials are fully stoppered and then capped. Media fill data is provided to support the aseptic filling process. The filled syringes are then visually inspected, packaged, stored, secondary packaged and stored again. The batch numbering system has been described and is considered adequate.

Process controls

The control strategy consists of process parameters (PPs) which are categorised as either critical (CPP), key (KPP), or non-key (NKPP) process parameters. The process control strategy also includes in-process tests which are divided into CIPCs, IPCs, and IPM.

Process Validation

To validate the finished product manufacturing process, three batches were manufactured at commercial scale. The validation consisted of process performance qualification (PPQ) run, shipping validation, media fill validation, sterile filter validation and cleaning validation.

The manufacturing process was appropriately validated with the majority of process parameters meeting specification.

There are hold times listed throughout the manufacturing process which were challenged beyond the proposed limit listed in section P.3.3 and P.3.4 during the PPQ runs.

Shipping validation was performed using shippers and number of boxes consistent with what will be used during the commercial process. A table has been presented which determined if the batches passed the acceptance criteria and acceptable range.

Media fill studies were carried at the manufacturing site. The media fill studies covered the maximum hold times and there was no growth detected in any of the vials tested.

Filter validation studies were performed that showed filter compatibility with the product. Extractable substance studies were performed at identical or worse case conditions than the normal filtration process. The data has been provided.

Product specification, analytical procedures, batch analysis

Specifications

The batch release and stability specifications are generally appropriate and address general properties (appearance, pH, osmolality), identity, quantity, purity, potency and safety related testing (bacterial endotoxins, sterility, CCIT).

The panel of release tests covers relevant aspects of purity, potency and safety. The proposed release tests are in line with the expectations of ICH Q6B and the Ph. Eur. monograph on monoclonal antibodies and cover the identified CQAs.

The applicant has outlined their approach for establishing specification acceptance criteria in the dossier which is based in accordance with ICH Q6B.

The acceptance criteria are all acceptable for a biological product.

Analytical procedures

The analytical procedures are either the same as for the active substance or pharmacopeial. Validation of these methods has been appropriately demonstrated. However, as the finished product vial formulation contains a combination of a surfactant and a chelator, studies investigating Low Endotoxin Recovery (LER) has been provided and shows no LER. A mitigation strategy has been provided and is deemed acceptable.

Batch analysis

Batch analysis data is provided for primary stability/process validation batches representative of the commercial process, phase III clinical batches and Phase I clinical batches. Batches were tested according to the specification in use at time of development. All batches met the acceptance criteria at the time of development. The changes made to the acceptance criteria for each specification has been highlighted.

Reference materials

The reference standard used for finished product is the same as that for active substance.

Characterisation of impurities

The applicant states no new impurities have been introduced during manufacture of the finished product. The risk assessment is stated to be aligned with the principles outlined in CHMP's Article 5 (3) opinion EMEA-H-A5(3)-1490. Risk for elemental impurities as per ICH Q3D is also provided and is acceptable.

Container closure

The container closure consists of a sterilised and depyrogenated Type I borosilicate glass vial, stoppered with a sterilised stopper and sealed with a cap. The description of the components and the suppliers of each component is brief but adequate. A schematic and specifications have been provided,

the specifications are considered appropriate. Both the vial and stopper are sterilised using conditions compliant with the requirements of Ph. Eur. 5.1.1 and the EMA/CHMP/CVMP/QWP/850374/2015.

Stability of the product

Stability data up to at the long-term storage condition of 2-8°C and the accelerated condition of 25 ± 2°C/65 ±5% are provided for at least three phase III batches and PPQ batches to support the proposed shelf life. The batches have been stored in the exact container as described in section P.7.

An in-use stability study was conducted to evaluate the compatibility with the injection device. As due to the syringe not provided by the applicant, the result of syringe dependent is not pursued.

A photostability was done in accordance with option 2 of ICH Q1B. The results indicate the product is light sensitive but when placed in the commercial packaging (carton box), this degradation is not observed.

The shelf-life is proposed as 5°C ± 3°C for up to 36 months, protected from light by outer packaging. The proposed shelf-life is deemed acceptable. Any extension of shelf life will require a variation. The proposal that an unopened vial may be stored outside the refrigerator is supported based on the accelerated data.

Biosimilarity

In general, a well-established biosimilarity exercise has been conducted as per the relevant EU guidelines on the development of similar biological medicinal products (CHMP/437/04 Rev 1, EMA/CHMP/BWP/247713/2012), as well as the principles of comparability as per ICH Q5E. Overall, the selection of batches is agreeable. The applicant has confirmed that all batches of RefMP used in the comparative assessment were stored and handled as per the approved conditions.

The attributes included in the comparative assessment cover the relevant attributes for a product of this nature and were analysed using a comprehensive set of orthogonal state-of-the–art analytical methods. The applicant has demonstrated that the analytical methods used in the biosimilarity study are suitable for their intended use.

The statistical approach to setting the acceptance criteria for the high and medium risk attributes is endorsed. The applicant applied an acceptance range respectively. For lower ranked attributes the applicant used fewer batches and applied a qualitative approach. This is endorsed.

Overall, ALT-L9 was found to be highly similar to Eylea.

The results of experimentally determined extinction coefficients are provided. A summary of the biosimilarity exercise is presented in Table 1.

To evaluate the similarity of ALT-L9 in comparison to RefMP, an analytical similarity assessment was performed.

Brief summary of the identified peptide fragments from individual digestion techniques was provided. Based on the data it is concluded that the higher order structure of the products is highly similar.

Molecular heterogeneity was characterised for size and charge heterogeneity as well as for further modifications. Results indicate similar structural, size, and charge heterogeneity, in further functional characterisation it was demonstrated that differences in N-glycosylation profile do not have impact on relevant biological properties and potency. Characterisation of the potential Fc-mediated effector

functions and biding affinities is considered adequate, and results are considered similar to the EU-sourced Eylea reference product.

Table 1. Summary of Eyluxvi analytical biosimilarity exercise

Attribute		**Method**	**Similarity Conclusion**
VEGF Related biological activities	Neutralisation	Cell-based Bioassay (anti-VEGF-A_{165}, anti VEGF-A_{110}, VEGF-A_{121}, VEGF-A_{189}, VEGF-A_{206}, VEGF-B_{167}, VEGFC, VEGF-D, or P1GF-2)	The results of VEGF-A_{165} binding assay of ALT-L9 were within the quality range. Similar. ALT-L9 and Eylea exhibited similar biological activity toward VEGF-A_{110}, VEGF-A_{121}, VEGF-A_{165}, VEGF-A_{189}, VEGF-A_{206}, VEGF-B, PlGF-1, and PlGF-2. As it is known that aflibercept does not bind to VEGF-C, and VEGF-D, no inhibition and no binding to these isoforms were observed with either ALT-L9 or Eylea.
	Ligand Binding	VEGF-A_{165} binding assay by ELISA, Anti-VEGF A_{110}, VEGF-A_{121}, VEGF-A_{165}, VEGF-A_{189}, VEGF-A_{206}, VEGFB_{167}, VEGF-C, VEGF-D, P1GF-1, or P1GF-2 by SPR, galectin-1 by ELISA	Similar. ALT-L9 and Eylea exhibited similar biological activity toward VEGF-A_{110}, VEGF-A_{121}, VEGF-A_{165}, VEGF-A_{189}, VEGF-A_{206}, VEGF-B, PlGF-1, and PlGF-2. As it is known that aflibercept does not bind to VEGF-C, and VEGF-D, no inhibition and no binding to these isoforms were observed with either ALT-L9 or Eylea.
	HUVEC antiproliferation	HUVEC anti-proliferation assay (anti-VEGF-A_{110}, VEGF-A_{121}, VEGF-A_{165}, VEGF-A_{189}, VEGF-A_{206}, VEGF-C, VEGF-D, or P1GF-2)	Similar. ALT-L9 and Eylea exhibited similar biological activity toward VEGF-A_{110}, VEGF-A_{121}, VEGF-A_{165}, VEGF-A_{189}, VEGF-A_{206}, VEGF-B, PlGF-1, and PlGF-2. As it is known that aflibercept does not bind to VEGF-C, and VEGF-D, no inhibition and no binding to these isoforms were observed with either ALT-L9 or Eylea.
Fc-related biological activities	FcRn binding	FcRn binding by SPR	Similar. ALT-L9 and Eylea has similar binding affinities to Fc receptors
	FcγRI binding	FcγRI binding by SPR	
	FcγRIIa binding	FcγRIIa binding by SPR	
	FcγRIIb binding	FcγRIIb binding by SPR	
	ADCC	ADCC Assay	Similar. Both ALT-L9 and Eylea exhibit no ADCC and CDC activity.
	CDC	CDC Assay	
	C1q	C1q binding by ELISA	Similar. ALT-L9 and Eylea exhibited similar binding properties for the C1q.
Quantity	Protein concentration	UV/Vis at A280	The results of protein concentration of ALT-L9 were within the quality range for Eylea.

Charge Variants	Acidic and basic variants	cIEF, AEX	Charge variants of ALT-L9 were within the quality range and the applicant has performed a biological activity study on the individual variants
	pI	cIEF	pI of ALT-L9 were within the quality range
Physicochemical properties	HMW	SE-HPLC	HMW of ALT-L9 were within the quality range
	LMW	CE-SDS (non-reducing)	LMW of ALT-L9 by CE-SDS (reducing and non-reducing) were within the quality range
	LMW	CE-SDS (reducing)	
	Product related impurities	Hydrophobic Interaction -HPLC	Similar. Peak 2 of ALT-L9 was slightly higher than Eylea, however, the difference was not significant considering assay variability. Therefore, hydrophobicity of ALT-L9 and Eylea were similar to each other
Particulates	Particulate matter (quantification, visualisation, quantification and visualisation)	DLS, MFI	Similar
Structural characterisation: Primary structure	Molecular weight (intact)	MALDI-TOF	Similar. Molecular weights of the intact and deglycosylated forms were analysed using MALDI-TOF and Q-TOF under both reducing and non-reducing conditions. Observed molecular weight of ALT-L9 and Eylea was almost identical with expected molecular weight of aflibercept and similar each other.
	Molecular weight (deglycosylated)	Q-TOF	
	Amino acid sequence	LC-ESI-MS/MS	Similar. The sequence coverage of ALT-L9 and Eylea are 100% in both peptide mapping and full-length sequencing.
	Amino acid composition	UPLC-FLD after hydrolysis	Similar. The amino acid composition of ALT-L9 and Eylea was consistent with the theoretical composition of aflibercept

	N-terminal sequence	LC-ESI-MS/MS	Similar. Both ALT-L9 and Eylea exhibited intact N-term peptide with 100% population. For C-term sequencing, Lys-deleted form is dominant in both ALT-L9 and Eylea, and relative contents of Lys-deleted form are similar each other.
	C-terminal sequence	LC-ESI-MS/MS	
	Oxidation	LC-ESI-MS/MS	Similar. Seven oxidation sites were observed in both ALT-L9 and Eylea, and the predominant oxidation of ALT-L9 and Eylea occurred at Met_{10}. Although the oxidation level at Met_{10} of Eylea was slightly higher than that of ALT-L9, however, it is deemed not to be a significant difference, considering assay variation.
	Dehydration	LC-ESI-MS/MS	Similar. Eleven dehydration sites were observed in both ALT-L9 and Eylea, and predominant dehydration of ALT-L9 and Eylea occurred at Asp_{234} and Asp_{297} with little variation
	Deamidation (Iso-Asp)	RP-HPLC (Iso-Asp)	Similar. Nine deamidation sites were observed in both ALT-L9 and Eylea, and the predominant deamidation of ALT-L9 and Eylea occurred at Asn_{84} and Asn_{99}. Although the deamidation level at Asn_{84} and Asn_{99} of Eylea were slightly higher than that of ALT-L9.
Structural characterisation: Higher Order Structure	Far- and near-UV CD	Far- and near-UV CD	Similar. ALT-L9 and Eylea exhibited similar CD spectra in both the far and near UV regions, indicating a similar secondary structure composition. Additionally, the local environments of their aromatic acid residues were observed to be highly similar.
	UV spectroscopy	UV spectroscopy	Similar. ALT-L9 and Eylea exhibited almost identical UV absorption spectra, indicating a similar composition and similar conformational environments of UV absorbing amino acid residues.
	FTIR Spectroscopy	FTIR Spectroscopy	Similar. ALT-L9 and Eylea exhibited almost identical FT-IR spectra, with closely matching maximum

			wavenumbers and absorbances in both amide I and II regions
	Intrinsic fluorescence spectroscopy	Intrinsic fluorescence spectroscopy	Similar. Both emission and excitation spectra of ALT-L9 and Eylea were highly overlapped, indicating the local environment around the fluorophores are highly similar.
	Thermodynamic stability	DSC	Similar. The DSC thermograms were highly similar to one another and exhibited two major transitions, which centred at near 67°C and 85°C, respectively
	Disulphide bond	LC-ESI-MS/MS	Similar. All Cys residues in both ALT-L9 and Eylea were linked by ten disulphide bonds (four intra-chain linked via one disulphide bond, one inter-chain linked via two disulphide bond) and there was practically no free Cys residue
	Free thiol	Free thiol group quantification assay kit	
Structural characterisation: Carbohydrate structure	N-linked glycosylation site determination	LC-ESI-MS/MS	Similar. 29 N-glycans were identified at five N-glycosylation sites (Asn_{36}, Asn_{68}, Asn_{123}, Asn_{196}, Asn_{282}). Except for glyco-peptide Asn_{123}, the most abundant N-glycan on each glyco-peptides was the same for both ALT-L9 and Eylea. At Asn_{123}, abundant N-glycan of ALT-L9 (aflibercept) was Man5, whereas for Eylea, it was G2+SA. The second most abundant N-glycan, both ALT-L9 (aflibercept) and Eylea have Man5 and G2+SA as their abundant N-glycans but found not to affect its biological activity. N-glycan profiles of ALT-L9 and Eylea are considered N-glycan to be similar each other.
	N-glycan identification	LC-ESI-MS/MS	
	O-glycan identification	LC-ESI-MS/MS	Similar. The O-glycosylation site occupancy was less than 0.1% for both ALT-L9 and Eylea
	Galactosylation	LC-ESI-MS/MS with 2-AB labelled glycans	Similar. The relative content of N-glycan species (galactosylation, sialylation, mannosylation, afucosylation) was similar between ALT-L9 and Eylea
	Mannosylation	LC-ESI-MS/MS with 2-AB labelled glycans	

	Afucosylation	HPLC-UV	
	Sialylation	HILIC-UPLC (FLD) or LC-ESIMS/MS with 2-AB labelled glycans	Similar. Molar contents of Neu5Ac of ALT-L9 and Eylea were similar to each other, and no Nue5Gc contents was observed.
	Monosaccharide	Bio-LC after hydrolysis	Similar. Monosaccharide contents in ALT-L9 and Eylea were similar to each other

Adventitious agents

A TSE risk assessment has been performed in accordance with guideline EMEA/410/01 "Note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medical Products". Although no materials of animal origin are used in the manufacture of the MCB, WCB, active substance or finished product, animal-derived materials were used during cell line development. The information provided in respect of TSE risk of these materials is considered acceptable and the risk is considered low.

Viral testing of the MCB, WCB and post-production cell bank (PPCB) was performed in accordance with EMEA/CHMP/BWP/398498/2005, ICH Q5A(R1) and ICH Q5D. The results are considered acceptable. The unprocessed bulk is routinely tested for the detection of adventitious viruses and CHO-K1 cell lines and separately for minute virus of mice (MVM). Batch analysis presented indicate that viral contaminants have not been detected in the unprocessed bulk. Control of vial adventitious agents is considered acceptable.

Viral clearance validation has been conducted in line with ICH Q5A. Viral clearance validation was conducted on three steps, as these were deemed to be orthogonal purification mechanisms, mitigating any potential over estimation of clearance. The choice of model viruses is typical for a CHO-derived product and includes a range of enveloped/non enveloped, genomes, sizes and shapes. The choice of model viruses is considered acceptable. All viral clearance steps evaluated gave a reproducible reduction for each model virus, which is deemed effective in line with ICH Q5A. The reduction factors presented demonstrate that the process is capable of removing substantially more virus that is potentially present based on the calculated safety factor for a single dose equivalent of unprocessed bulk.

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

The active substance ALT-L9 (aflibercept) is a recombinant fusion protein consisting of the second immunoglobulin (Ig) domain of the human vascular endothelial growth factor receptor (VEGFR)-1 and the third Ig domain of the human VEGFR-2, with both polypeptide chains fused to the Fc domain of human IgG1. It is produced by recombinant DNA technology in a mammalian cell (Chinese hamster ovary [CHO-K1]) culture and purified through the downstream process. The active substance manufacturing process is standard for the production of a recombinant protein. Lists of raw materials have been provided. Details of developmental genetics and the establishment of the MCB and WCB are described and are acceptable. The control strategy for the active substance is comprehensive. The manufacturing process has been appropriately validated. The process development data was comprehensive.

The characterisation data presented was comprehensive. The panel of release tests covers relevant aspects of purity, potency, and safety. However, several queries have been raised regarding the critical reagents. Batch data provided demonstrate that the commercial process is capable of manufacturing a consistent active substance. Reference standards are adequately described.

The container closure system for the active substance is a ready-to-use, sterile, Biotainer bottle. Some points for clarification regarding compliance with the EMA guideline on plastic immediate packaging materials and extractables are raised. The proposed shelf-life for ALT-L9 active substance is when stored at freeze. The data presented supports the proposed shelf life.

The formulation studies demonstrate the commercial composition is suitable to maintain the quality of the finished product which is supported by stability data. The manufacturing process is standard for a monoclonal antibody. The control strategy for the finished product is comprehensive with sufficient control of each manufacturing step. Validation data has been presented on process performance qualification batches and shows the manufacturing process with the proposed control strategy is capable of producing finished product of a consistent quality. The panel of release tests covers relevant aspects of purity, potency and safety. The batch data demonstrates that the commercial process is capable of manufacturing a consistent finished product.

The container closure consists of a Type I borosilicate glass vial, stoppered with a stopper and sealed with a cap. A shelf-life protected from light at 2-8°C is deemed acceptable based on the data provided. The proposal that an unopened vial may be stored outside the refrigerator below 25°C for up to 24 hours is also deemed acceptable.

The adventitious agents' safety evaluation is acceptable.

A comprehensive analytical exercise was performed to evaluate ALT-L9 similarity with EU-Eylea reference medicinal product in all relevant physical and chemical attributes and functional characteristics. Eyluxvi is consider biosimilar to EU-Eylea from a quality point of view.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance and intermediates is adequately described, controlled and validated. The active substance and intermediates are well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

Overall, the quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

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

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Eyluxvi (ALT-L9) has been developed as a proposed biosimilar product of Eylea (aflibercept) for the same use with respect of administration (intravitreal (IVT) injection), and therapeutic indications approved for Eylea 40 mg/mL solution for injection in a vial.

The active ingredient of ALT-L9, aflibercept, is synthesised by Chinese hamster ovary (CHO) K1 cells as a dimeric, secreted, soluble protein and suitably purified. Aflibercept is a highly purified 864 amino acid (2 X 432 amino acids) recombinant protein consisting of sequences derived from Ig domain 2 of human Vascular endothelial growth factor receptor 1 (VEGFR1), Ig domain 3 of VEGFR2 and the Fc portion of human IgG1. The primary amino acid sequences of ALT-L9 and Eylea have been shown to be identical.

The nonclinical development programme includes *in vitro* analytical similarity studies to evaluate the biological properties of ALT-L9 and to demonstrate its biosimilarity to Eylea. In order to comply with regulations in other jurisdictions, various *in vivo* studies using Eylea were performed. These included a comparative *in vivo* efficacy assessment in a rabbit model of choroidal neovascularisation (CNV), two single-dose studies in rabbits (PK and tissue distribution) and a GLP-compliant 13-week repeat-dose toxicity including toxicokinetic (TK) and immunogenicity assessment in cynomolgus monkeys.

The conduct of *in vivo* pharmacodynamic, single-dose or repeat-dose toxicity studies is not required for filing a biosimilar marketing authorisation application (MAA) in the EU and is usually not recommended (in accordance with relevant EMA guideline (EMA/CHMP/BMWP/403523/2010) and scientific advice (EMA/SA/0000063713). Therefore, the *in vivo* data provided were assessed as complementary information.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

In order to demonstrate biosimilarity between ALT-L9 and the reference medicinal product (RefMP), Eylea, the applicant performed a number of in vitro pharmacology assessments to compare biological properties (VEGF- or Fc-related) of ALT-L9 and Eylea as part of quality evaluation.

The details of the analysis performed, and the similarity outcome are summarised below (Table 2):

Table 2. Analyses performed

Assessment	Protein Targets	Details of Analysis	Similarity Outcome
VEGF related biological activity	VEGF-A_{110}	To evaluate binding properties of ALT-L9 and Eylea to VEGF isoforms or VEGF-related ligands, PathHunter® neutralisation assay, HUVEC anti-proliferation assay, SPR or ELISA were conducted. ALT-L9 and Eylea exhibited similar biological activity towards VEGF-A_{110}, -A_{121}, -A_{165}, -A_{189}, -A_{206}, -B, PlGF-1 and PlGF-2. ALT-L9 and Eylea	ALT-L9 and Eylea showed similar
	VEGF-A_{121}		
	VEGF-A_{165}		
	VEGF-A_{189}		
	VEGF-A_{206}		

	VEGF-B VEGF-C VEGF-D PlGF-1 PlGF-2 Galectin-1	showed no inhibition and no binding to VEGF-C and -D, isoforms. ALT-L9 showed slightly lower binding affinity to galectin-1 compared to Eylea. Considering the inherent variability in biological activity assay and binding to galectin-1 is defined through its carbohydrate recognition domain, not a specific motif, this difference is considered to be non-meaningful.	VEGF related biological activity
Fc-related Biological Activities	FcγRI FcγRIIa FcγRIIb FcγRIIIa FcγRIIIb FcRn	To evaluate binding properties of ALT-L9 and Eylea to Fc receptors, SPR analysis were performed. ALT-L9 and Eylea had similar affinities to Fc receptors. ALT-L9 showed slight variability in FcRn binding affinity, but was considered to be minor, since systemic exposure of aflibercept is minimal and FcRn binding affinity variations have minimal impact on ocular pharmacokinetics	ALT-L9 and Eylea showed similar Fcγ and FcRn related binding properties
	C1q	Affinities to C1q were analysed by ELISA. ALT-L9 and Eylea exhibited similar binding properties for C1q	ALT-L9 and Eylea showed similar C1q binding properties
	ADCC CDC	ADCC, CDC assay was performed to examine cytotoxicity. It is known that aflibercept does not trigger the immunological mechanisms of ADCC and CDC. Both ALT-L9 and Eylea did not exhibit any ADCC and CDC activity	ALT-L9 and Eylea showed no ADCC and CDC activity

From a nonclinical perspective, the functional *in vitro* data package is deemed adequate for demonstrating the similar biological activity of ATL-L9 and Eylea and reflects the principal mode of action of aflibercept.

In general, ATL-L9 appears to exhibit similar VEGF-related and Fc-related biological activities as the RefMP, Eylea. However, ALT-L9 showed slightly lower binding affinity for galectin-1 compared to Eylea. Considering the inherent variability in biological activity assay and that binding to galectin-1 is defined through its carbohydrate recognition domain, not a specific motif, the applicant considered this difference to be non-meaningful. ALT-L9 also showed slight variability in FcRn binding affinity. The applicant considered this variability to be minor, since systemic exposure of aflibercept is minimal and FcRn binding affinity variations have minimal impact on ocular pharmacokinetics and this is agreed. All in vitro functional studies were included in quality part of dossier and are presented and reviewed in more detail under Quality/Biosimilarity section.

The applicant also presented an *in vivo* comparative efficacy assessment of ALT-L9 and Eylea in a rabbit model of CNV. Following a single administration of ALT-L9 and Eylea via IVT injection, similar angiogenesis-inhibitory effects were observed.

Since the assessment of biosimilarity of ALT-L9 was primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted and the *in vivo* study was not deemed necessary, the *in vivo* results are used as complementary evidence.

2.3.2.2. Secondary pharmacodynamic studies

No secondary PD studies were conducted. The lack of secondary PD studies is considered acceptable for an application under Article 10(4) of Directive 2001/83/EC and in accordance with Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1).

2.3.2.3. Safety pharmacology programme

No safety pharmacology studies were conducted. The lack of safety pharmacology studies is considered acceptable for an application under 10(4) of Directive 2001/83/EC and in accordance with EMEA/CHMP/BMWP/42832/2005 Rev 1 guideline.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted. The lack of pharmacodynamic drug interaction studies is considered acceptable for an application under Article 10(4) of Directive 2001/83/EC and in accordance with EMEA/CHMP/BMWP/42832/2005 Rev 1 guideline.

2.3.3. Pharmacokinetics

The comparative pharmacokinetic (PK) profiling included non-GLP single dose studies in rabbits (PK and tissue distribution) and toxicokinetic (TK) evaluation performed as part of GLP 13-week pivotal repeat-dose toxicity study in monkeys (see section 2.3.4.6 for more details on TK data). ALT-L9 and Eylea were administered by IVT route. New Zealand White Rabbits, Dutch Belted Rabbits and Cynomolgus Monkeys were chosen as relevant species. The electrochemiluminescence (ECL) method was developed and sufficiently validated for the quantitation of ALT-L9 and Eylea in non-human primate vitreous humour, plasma and for the detection of anti-ALT-L9 antibodies in non-human primate serum. Validation of the ECL methods was conducted in compliance with GLP. Inter- and intra-assay precision and accuracy were acceptable.

In a non-GLP compliant study (18-KE-192), the exposure of ALT-L9 and Eylea were similar with respect to C_{max}, AUC and clearance in vitreous humour, plasma, aqueous humour and retina/choroid protein. However, the T_{max} was higher following ALT-L9 administration compared to Eylea administration in the vitreous humour and retina/choroid protein.

In a tissue distribution study where radiolabelled (I125)ALT-L9 and (I125)Eylea were administered via IVT to male Dutch Belted rabbits at a dose level of 2 mg/eye, there was only an n=1 per group per timepoint and therefore no statistical comparison between the groups was possible.

The *in vivo* PK studies provided by the applicant were conducted in support of global marketing authorisation for ALT-L9 and are generally not required for an EU MAA under Article 10(4) of Directive 2001/83/EC and EMEA/CHMP/BMWP/42832/2005 Rev. 1. The assessment of biosimilarity of ALT-L9 is primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted. Therefore, the *in vivo* studies using Eylea have been assessed as complementary information.

There were no metabolism, excretion, PK drug interaction or other PK studies conducted, as part of this application, and none are required in line with biosimilar development (Article 10(4) or Directive 2001/83/EC and Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

No single-dose toxicity study was performed. This is considered acceptable for an application under Article 10(4) of Directive 2001/83/EC and in accordance with EMEA/CHMP/BMWP/42832/2005 Rev1 guideline.

2.3.4.2. Repeat dose toxicity

The applicant provided a GLP-compliant 13-week repeat dose toxicity study in cynomolgus monkeys to compare the potential toxicity, TK and antigenicity profile of ALT-L9 relative to Eylea as the RefMP.

Several limitations were identified in this study. There was an acute, severe ocular reaction in the ALT-L9 treated cohort where five out of ten animals (7/20 eyes) developed severe uveitis and some did not recover by the time of scheduled sacrifice (Day 92). The ALT-L9 administered to this cohort was prepared in screw-top cryovials with internal caps. An additional ALT-L9 treated cohort was added where the administered ALT-L9 was prepared using septum-top vials and no ocular reactions were observed. The applicant suggested that this reaction was caused by the contamination of endotoxin in the screw-top cryovials. However, a definitive source of the contamination could not be determined. The subsequent comparison between Eylea treated animals and ALT-L9 group that was introduced at later time point is not optimal.

Overall, there were no ALT-L9-related (when prepared using septum-top vials) or Eylea-related effects on mortality, clinical observations, body weight, indirect ophthalmoscopy, slit-lamp biomicroscopy, intraocular pressure, and electroretinogram, clinical pathology parameters, microscopy observations, or organ weights. A treatment-related ophthalmic finding was observed in one female administered ALT-L9 (prepared in septum-top vials). The applicant considered this finding to be non-adverse due to minimal magnitude and lack of any degenerative/necrotic changes in any other ocular substructures. Two Eylea-treated male animals had minimal mononuclear infiltrates within the iris/ciliary body in either right or left eyes. Since similar findings were present in concurrent control animals, the applicant did not consider these findings as adverse.

The *in vivo* repeat-dose toxicity study provided by the applicant was conducted in support of global marketing authorisation for ALT-L9 and are generally not required for an EU MAA under Article 10(4) of Directive 2001/83/EC and EMEA/CHMP/BMWP/42832/2005 Rev. 1. The assessment of biosimilarity of ALT-L9 is primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted. Therefore, the *in vivo* studies using Eylea have been assessed as complementary information.

2.3.4.3. Genotoxicity

No genotoxicity or mutagenicity studies were performed. The lack of genotoxicity studies is in line with the guideline on biotechnology-derived pharmaceuticals ICH S6 (R1) as well as the EMA guideline on biosimilars medicinal products EMEA/CHMP/BMWP/42823/2005 Rev. 1. It is noted that the range and

type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals because large proteins would not be expected to pass through cell membranes and interact directly with DNA or other chromosomal material.

2.3.4.4. Carcinogenicity

No carcinogenicity studies were performed. This is acceptable and in line with the applicable guidelines (EMEA/CHMP/BMWP/42832/2005 Rev1 and ICH S6 (R1)). It is noted that studies regarding carcinogenicity are not required for non-clinical testing of biosimilars.

2.3.4.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were performed. This is acceptable and in line with the applicable guideline (EMEA/CHMP/BMWP/42832/2005 Rev1). The text for section 4.6 and 5.3 of the Summary of Product Characteristics (SmPC) is in line with the reference product.

2.3.4.6. Toxicokinetic data

Comparative TK assessments were performed as part of the GLP-compliant 13-week repeat-dose toxicity study in cynomolgus monkeys (see section 3.2.4.2 for more details and study limitations). The toxicokinetic analysis showed that the systemic exposure to ALT-L9 (prepared in septum-top vials) and Eylea were independent of sex. Mean concentrations of ALT-L9 (prepared in septum-top vials) and Eylea were generally similar. The analyte ratios based on mean $AUC_{(0\text{-}168h)}$ values were 1.21 on Day 1 and 1.12 on Day 85.The terminal and recovery concentrations of ALT-L9 (prepared in septum-top vials) and Eylea in vitreous humour were also similar following IVT injection.

2.3.4.7. Local tolerance

No dedicated local tolerance study was conducted. Ocular tolerance was evaluated in the 13-week repeat dose toxicity study. This is acceptable and in line with the applicable guideline EMEA/CHMP/BMWP/42832/2005 Rev1.

2.3.4.8. Other toxicity studies

Antigenicity

Blood samples for anti-drug antibody (ADA) analysis were collected during the GLP-compliant 13-week repeat dose toxicity study with 4-week recovery arm (see section 2.3.4.2 for more details and study limitations). One control female out of 12 control animals was positive for ADAs on Day 92. All recovery control animals were negative for ADAs on Day 119. One out of 10 (10%) animals treated with Eylea developed ADAs, whereas in ALT-L9 (prepared in septum-top vials)-treated group, 3 out of 10 (30%) animals developed ADAs. One of the ALT-L9 (prepared in septum-top vials)-treated recovery animal remained positive for ADAs at day 119It is acknowledged that the nonclinical immunogenicity data may not be predictive of the clinical situation.

2.3.5. Ecotoxicity/environmental risk assessment

ALT-L9 is a monoclonal antibody and is classified as a protein. Therefore, an environmental risk assessment (ERA) is not required for this medicinal product in accordance with the Guideline on the

environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1). An expert statement justifying the absence of an ERA has been submitted by the applicant. This is signed by Laura Lopez Fuertes, DVM, PhD, ERT and dated 23rd May 2024. A suitable brief CV is provided. The applicant's justification for the lack of an ERA is considered acceptable. 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, aflibercept is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

An abridged nonclinical package has been provided to support the MAA for ALT-L9 (Eyluxvi). This is acceptable considering the product is a biosimilar of Eylea for which there is extensive clinical experience.

Overall, the nonclinical *in vitro* functional activity data support the biosimilarity of ALT-L9 versus the EU approved RefMP, Eylea. In general, ATL-L9 appears to exhibit similar VEGF-related biological activities and Fc-related biological activities as the RefMP Eylea. However, ALT-L9 showed slightly lower binding affinity for galectin-1 compared to Eylea and slight variability in FcRn binding affinity. These *in vitro* functional studies were included in quality part of the dossier and are presented in more detail and reviewed under Quality/Biosimilarity section.

According to the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Revision 1' (EMEA/CHMP/BMWP/42832/2005 Rev1), when the assays support the similarity, animal studies are not deemed necessary. However, and despite the 3R's principles, the applicant presented studies, comparative against the reference product, in order to fulfil requirements of non-European regulatory bodies.

Briefly, the package consisted of comparative studies of pharmacology (Chinchilla rabbit, single IVT dose, 500µg/eye), pharmacokinetics (New Zealand white rabbits, single IVT dose, 500µg/eye), ocular distribution (Dutch Belted rabbits, single IVT dose, 2 mg/eye) and toxicology (Cynomolgus monkeys, IVT administration once a week for four weeks, 2 mg/eye, GLP-compliant). As conduct of these *in vivo* comparative studies were not regulatory required to support an MAA in the EU, the *in vitro* studies are sufficient from a nonclinical perspective to attest to demonstrate similarity between ALT-L9 and the RefMP, Eylea. Therefore, the assessment of biosimilarity is primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted.

No genotoxicity, carcinogenicity, developmental and reproductive or other toxicity studies have been carried out with ALT-L9 and none are required in line with biosimilar development (Article 10(4) of Directive 2001/83/EC and EMEA/CHMP/BMWP/42832/2005 Rev. 1 guideline).

Adequate justification for absence of ERA has been provided. Monoclonal antibodies are unlikely to pose a significant risk to the environment. Environmental risk assessment studies are therefore not required in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1).

Sections 4.6 and 5.3 of the SmPC are in line with the reference product.

2.3.7. Conclusion on the non-clinical aspects

Overall, the available nonclinical *in vitro* studies support the MAA of ALT-L9 and are in compliance with legislation from EU as well as the biosimilar relevant guidance from the EMA. There are no objections to the approval of ALT-L9 (Eyluxvi) from a nonclinical perspective. The assessment of biosimilarity is

primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted. The *in vivo* pharmacodynamic, pharmacokinetic and toxicology studies were conducted in support of global marketing authorisation for ALT-L9 and are not required for the MAA in the EU in accordance with relevant guidance from the EMA and CHMP scientific advice. The design of the nonclinical package required for MAA of biosimilar products is deemed adequate.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

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

Table 3. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Healthy Subjects or Diagnosis of Patients	Number of Subjects (Randomized)	Study Status; Type of Report
Efficacy, Safety, PK	ALT-L9-01	Module 5.3.5.1	To evaluate the safety, efficacy and PK characteristics of ALT-L9 following a total of 3 doses at 4-week intervals for 16 weeks in subjects with neovascular (wet) AMD	Phase 1, multicenter, double-masked, randomized, active-controlled, parallel-group study	ALT-L9 or EYLEA (2 mg) in the study eye by IVT injection once every 4 weeks for 8 weeks in the treatment period for a total of 3 doses Total duration (excluding screening): 16 weeks (treatment period: 8 weeks, follow-up period: 8 weeks)	Neovascular age-related macular degeneration (wet AMD)	28	Complete; Full
Efficacy, Safety, PK	ALT-L9-03	Module 5.3.5.1	To demonstrate that the biosimilar candidate ALT-L9 2 mg/50 µL is equivalent to Eylea (aflibercept), as well as to evaluate the safety, efficacy, systemic exposure, and immunogenicity of ALT-L9 compared with Eylea in subjects with neovascular (wet) AMD	Phase 3, multicenter, double-masked, randomized, active-controlled, parallel-group study	ALT-L9 or EYLEA (2 mg) in the study eye by IVT injection once every 4 weeks for 8 weeks and then once every 8 weeks for 40 weeks in the treatment period for a total of 8 doses Total duration (excluding screening): 52 weeks (treatment period: 48 weeks, follow-up period: 4 weeks)	Neovascular age-related macular degeneration (wet AMD)	431	Complete; Full

2.4.2. Clinical pharmacology

The clinical development programme for ALT-L9 (aflibercept) consists of a Phase 1 study (ALT-L9-01) and a Phase 3 study (ALT-L9-03) and aims to support the registration of ALT-L9 (aflibercept) in the EU as a biosimilar to Eylea. The pharmacokinetic (PK) objective of these studies aimed to compare the PK of the test (ALT-L9) and reference (Eylea) products by analysing the plasma concentration of aflibercept in both studies. A summary of the clinical studies can be found in Table above.

2.4.2.1. Pharmacokinetics

Bioanalytical methods

In general, the methods used to measure human serum levels of the aflibercept active substance of ALT-L9 and Eylea, and anti-drug antibodies (ADA) for the Phase I study have not been fully validated

in line with ICH guideline M10 on bioanalytical method validation EMA/CHMP/ICH/172948/2019. However, as the phase I study ALT-L9-01 is supportive only no queries are raised. The bioanalytical methods used during the Phase III study include methods for measuring human serum levels of the active substance of ALT-L9 and Eylea, anti-drug antibodies (ADA), and neutralising antibodies (NAb). It is agreed that these methods have been suitably validated in line with the relevant guidelines.

Absorption

Bioequivalence

Based on current evidence it was agreed that it is unlikely that the systemic concentration of aflibercept after intravitreal injections would be high enough to exert a clinically relevant systemic effect. Therefore, it was agreed that a dedicated study to demonstrate PK similarity assessment between ALT-L9 and RefMP in healthy subjects is not needed.

However, whether systemic exposure levels are within a similar range as for the reference product will need to be adequately shown also for the proposed biosimilar ALT-L9 by providing adequate PK data. The applicant has performed two studies in the target population (ALT-L9-01 and ALT-L9-03) and provided PK analyses in these subjects.

Pharmacokinetics in the target population

Study ALT-L9-01

Design

This was a Phase 1, randomised, double-masked, active-controlled, parallel-group study in patients (planned N=30) ≥50 years of age with neovascular (wet) AMD. The PK objective of this study was to evaluate the pharmacokinetic (PK) characteristics of the test drug ALT-L9 following the first of the 3 total doses administered in the study.

Blood samples for measuring plasma concentrations of aflibercept were collected serially at the following time points: pre-dose, 3 hours, and 1, 7, and 28 days after the first dose. The plasma concentration-time profiles of aflibercept following IVT administration of Eylea® and ALT-L9 were plotted in a linear or log/linear (semi log) graph.

Non-compartmental methods were used to estimate the PK parameters $t_{1/2}$, C_{max}, T_{max}, C_{last}, AUC_{last}, $AUC_{infinity}$, CL/F, and V_d/F. The independent t-test was applied to compare the PK parameters between the groups, and the probability value (p-value) to determine statistical significance was set to 0.05.

Results

The mean plasma concentration of aflibercept demonstrated no statistically significant differences in PK parameters with or without the subject with unexpectedly high exposures between the Eylea and ALT-L9 groups (Table 4).

Table 4. Geometric mean (± GeoSD) and statistical comparison for aflibercept PK parameters after IVT injection of Eylea and ALT-L9, with and without inclusion of a subject with higher exposures

Parameter	Including a Subject with Higher Exposure			Excluding a Subject with Higher Exposure		
	Eylea	ALT-L9	*p*-value	Eylea	ALT-L9	*p*-value
$t_{1/2}$ (day)	18.0 ± 1.4	17.6 ± 1.6	0.795	18.0 ± 1.4	19.0 ± 1.5	0.562
T_{max} (day)	1.1 ± 1.7	1.1 ± 2.6	0.621	1.1 ± 1.7	1.3 ± 2.1	0.515
C_{max} (ng/mL)	30.6 ± 1.5	39.7 ± 2.3	0.277	30.6 ± 1.5	33.0 ± 1.7	0.529
C_{last} (ng/mL)	8.9 ± 1.2	9.8 ± 1.1	0.161	8.9 ± 1.2	10.0 ± 1.1	0.102
$AUC_{0\text{-}28d}$ (ng•day/mL)	396.3 ± 1.3	464.7 ± 1.3	0.144	396.3 ± 1.3	436.4 ± 1.2	0.258
$AUC_{infinity}$ (ng•day/mL)	645.1 ± 1.2	760.1 ± 1.2	0.062	645.1 ± 1.2	737.2 ± 1.2	0.119
V_d/F (L)	80.6 ± 1.4	67.0 ± 1.6	0.289	80.6 ± 1.4	74.3 ± 1.4	0.482
CL/F (L/day)	3.1 ± 1.2	2.6 ± 1.2	0.059	3.1 ± 1.2	2.7 ± 1.2	0.103

GeoSD = geometric standard deviation; IVT = intravitreal; PK = pharmacokinetic.

Descriptive summaries of plasma PK parameters for the first dose for each treatment are presented in Table 5. The slightly higher geometric mean PK exposures observed for ALT-L9 (aflibercept) compared to Eylea are likely attributable to one subject. With higher exposures in the ALT-L9 (aflibercept) group (AUC parameters for this subject were approximately 1.5- to 2-fold higher and C_{max} was approximately 11-fold higher compared to the geometric mean values for the ALT-L9 group. Exclusion of this subject from descriptive statistics resulted in similar geometric mean PK exposure parameters for the two treatments (geometric mean C_{max} of 33.0 ng/mL versus 30.6 ng/mL and geometric mean $AUC_{0\text{-}28d}$ of 436 day*ng/mL versus 396 day*ng/mL for ALT-L9 (aflibercept) compared to Eylea treatment the geometric coefficient of variation (%GCV) for C_{max} decreased from 103.2% to 54.6%.

Table 5. Geometric mean (%GCV) single-dose aflibercept plasma PK parameters for each treatment (PK analysis set)

PK Parameter	ALT-L9 (Aflibercept) (N = 14)	EYLEA (N = 14)	*P*-value [d]
C_{max} (ng/mL)	39.7 (103.2) [b] 33.0 (54.6) [c]	30.6 (42.2)	0.277
$AUC_{0\text{-}28d}$ (day*ng/mL)	465 (28.6) [b] 436 (15.9) [c]	396 (23.5)	0.144
$AUC_{infinity}$ (day*ng/mL)	760 (22.4) [b] 737 (19.9) [c]	645 (21.7)	0.062
T_{max} (day) [a]	1.00 (0.13, 7.00) [b] 1.00 (1.00, 7.00) [c]	1.00 (1.00, 7.00)	N/A
C_{last} (ng/mL)	9.81 (12.7) [b] 9.97 (11.7) [c]	8.95 (19.1)	0.161
$t_{1/2}$ (day)	17.6 (52.6) [b] 19.0 (44.8) [c]	18.0 (32.6)	0.795
CL/F (L/day)	2.63 (22.4) [b] 2.71 (19.9) [c]	3.10 (21.7)	0.059
V_d/F (L)	67.0 (51.6) [b] 74.3 (31.1) [c]	80.6 (32.4)	0.289

%GCV = geometric coefficient of variation (percent); N = number of subjects included in the PK Analysis Set for each treatment; N/A = not applicable; PK= pharmacokinetic.
Geometric means are reported to 3 significant digits and %GCV is reported to 1 decimal place. T_{max} is reported to 2 decimal places.
[a] Values presented are median (minimum, maximum).
[b] Statistics include all subjects in the PK Analysis Set (N=14).
[c] Statistics include all subjects in the PK Analysis Set, except for one subject with high PK exposure (N=13).
[d] *P*-value for independent t-test to compare PK parameters between treatment groups (full PK Analysis Set).

Study ALT-L9-03

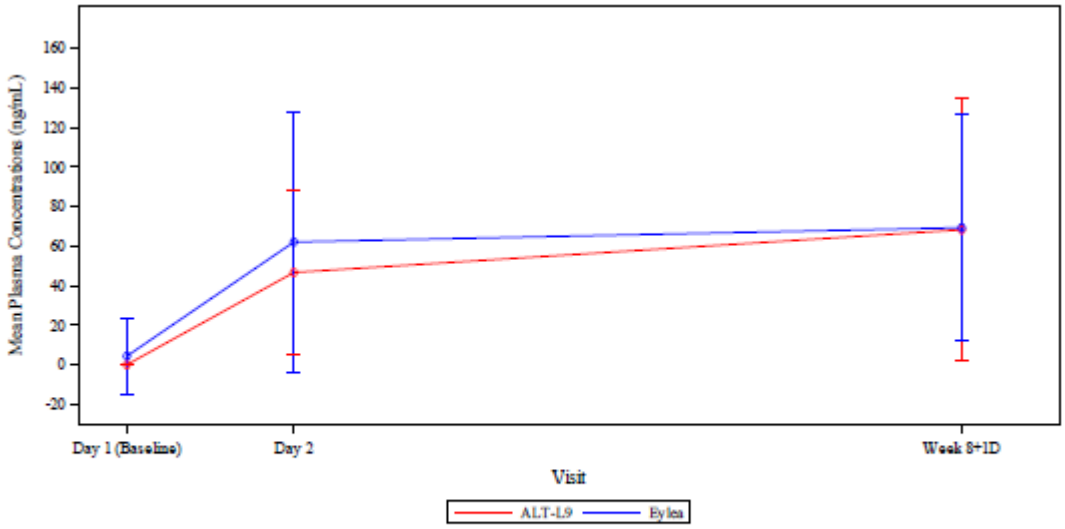
This was a randomised, double-masked, active-controlled, parallel-group, multicentre study in treatment-naïve patients with neovascular AMD (planned N=410; 205 per treatment arm) who were ≥50 years of age. The evaluation of the systemic exposure of ALT-L9 versus Eylea in subjects participating in the PK evaluation was included in this study as a secondary objective. The PK endpoint of this study was the plasma concentration of ALT-L9 versus Eylea at certain timepoints (at baseline and 24 hours after the first and third IVT injection).

A PK subgroup (40 planned subjects' total; 20 per treatment arm) had blood samples collected at pre-dose on Day 1, approximately 24 hours after the first dose (Day 2), and approximately 24 hours after the third dose (Day 58; Week 8 + 1 day) for plasma free (unbound) aflibercept concentration measurements. A sample size of 20 subjects per group was determined to be sufficient to produce a 2 sided 95% CI with a distance from the difference in mean (assumed to be 0) to the limits equal to 0.32 when the estimated SD for both treatments was equal to 0.52. This number of subjects was considered sufficient to provide some statistical inference based on CIs and descriptive statistics of the concentrations of ALT-L9 and Eylea.

Results

The plots of the mean aflibercept plasma concentrations over time for the ALT-L9 and Eylea treatments, over a linear scale, are presented in Figure 1.

Figure 1. Plasma concentrations – Mean values over time (linear scale) (pharmacokinetic set)



Abbreviation: BLQ, below the limit of quantitation.
Note: Plasma concentration BLQ values were treated as zero.
Plasma concentration of aflibercept were obtained at baseline (Day 1, predose), and on Day 2 and Day 58 (Week 8 + 1 day) for a total of 3 samples in a subset of subjects.

The geometric mean and geometric CV% of aflibercept plasma concentrations obtained from subjects treated with ALT-L9 and Eylea are summarised by geographic region in Table 6. Geometric mean concentrations measured at 24 hours post-dose (i.e., approximate Cmax) were slightly lower in the ALT-L9 (aflibercept) treatment group compared to the Eylea treatment group for the first dose (i.e., on Day 2), but were similar between treatments for the third dose (i.e., Day 58; steady state) (50.2 ng/mL for ALT-L9 [aflibercept] versus 54.5 ng/mL for Eylea treatment. When assessed by geographical region, geometric mean 24-hour post-dose aflibercept concentrations on Day 2 and Day 58 were similar between treatments for the European region.

Table 6. Summary of aflibercept plasma concentrations (ng/mL) (pharmacokinetic set)

Geographic Region	Visit	Statistic	ALT-L9 (N=25)	Eylea® (N=21)
Overall	Day 1 (Baseline)	n	23	20
		GM (GM CV%)	- (-)	87.050 (-)
	Day 2	n	25	21
		GM (GM CV%)	31.201 (123.7)	41.865 (113.2)
	Week 8 + 1 D	n	25	19
		GM (GM CV%)	50.232 (89.8)	54.466 (75.9)
Europe	Day 1 (Baseline)	n	20	16
		GM (GM CV%)	- (-)	- (-)
	Day 2	n	22	17
		GM (GM CV%)	33.188 (125.7)	33.026 (88.0)
	Week 8 + 1 D	n	22	15
		GM (GM CV%)	49.596 (69.8)	44.229 (55.2)
Asia Pacific	Day 1 (Baseline)	n	3	4
		GM (GM CV%)	- (-)	87.050 (-)
	Day 2	n	3	4
		GM (GM CV%)	19.842 (114.1)	114.701 (107.2)
	Week 8 + 1 D	n	3	4
		GM (GM CV%)	55.151 (417.4)	118.895 (76.5)

Abbreviations: CV, coefficient of variation; D, Day; GM, geometric mean; N, number of subjects in the Pharmacokinetic Set for each treatment group; n, number of subjects with available data.
Plasma samples were collected at predose on Day 1 (Baseline) and at 24 hours (±2 hours) on Day 2 and Week 8 + 1 D.
Note: Statistics represented as "-" due to 1 or fewer values above the lower limit of quantitation (5.00 ng/mL).

2.4.2.2. Pharmacodynamics

No specific pharmacodynamics studies were performed as part of this application.

Immunological events

ALT-L9-03

Immunogenicity was assessed by measuring ADA levels and NAbs in the serum of all subjects. Blood samples for ADA assessment were collected from all randomised and treated subjects at the timepoints defined in the Schedule of Assessments. Additional samples for the monitoring of immunogenicity were to be collected from subjects with any signs of intraocular inflammation, as these may indicate an immune reaction.

The immunogenicity endpoint is the serum concentration of ADAs and Nabs before treatment at Day 1, Week 4, Week 8, Week 16, Week 32, and Week 52.

A summary of ADA and NAb status by week and ADA titre by visit for the Safety Analysis Set is provided in Table 7 and Table 8, respectively.

Table 7. Summary of anti-drug antibody and neutralizing antibody status by week (safety analysis set)

Parameter	Visit	Statistics	ALT-L9 (N=216)	Eylea (N=215)	Overall (N=431)
ADA	Baseline	n	216	213	429
		Negative, n (%)	214 (99.1)	211 (99.1)	425 (99.1)
		Positive, n (%)	2 (0.9)	2 (0.9)	4 (0.9)
ADA status up to Week 4	Week 4	n	216	215	431
		ADA negative, n (%)	206 (95.4)	208 (96.7)	414 (96.1)
		ADA induced, n (%)	6 (2.8)	5 (2.3)	11 (2.6)
		ADA boosted, n (%)	0	0	0
		ADA positive without boosted, n (%)	2 (0.9)	2 (0.9)	4 (0.9)
		Missing[a], n (%)	2 (0.9)	0	2 (0.5)
ADA status up to Week 8	Week 8	n	216	215	431
		ADA negative, n (%)	166 (76.9)	163 (75.8)	329 (76.3)
		ADA induced, n (%)	46 (21.3)	50 (23.3)	96 (22.3)
		ADA boosted, n (%)	0	0	0
		ADA positive without boosted, n (%)	2 (0.9)	2 (0.9)	4 (0.9)
		Missing[a], n (%)	2 (0.9)	0	2 (0.5)
ADA status up to Week 16	Week 16	n	216	215	431
		ADA negative, n (%)	165 (76.4)	160 (74.4)	325 (75.4)
		ADA induced, n (%)	47 (21.8)	53 (24.7)	100 (23.2)
		ADA boosted, n (%)	0	0	0
		ADA positive without boosted, n (%)	2 (0.9)	2 (0.9)	4 (0.9)
		Missing[a], n (%)	2 (0.9)	0	2 (0.5)
ADA status up to Week 32	Week 32	n	216	215	431
		ADA negative, n (%)	162 (75.0)	157 (73.0)	319 (74.0)
		ADA induced, n (%)	50 (23.1)	56 (26.0)	106 (24.6)
		ADA boosted, n (%)	0	1 (0.5)	1 (0.2)
		ADA positive without boosted, n (%)	2 (0.9)	1 (0.5)	3 (0.7)
		Missing[a], n (%)	2 (0.9)	0	2 (0.5)
ADA status up to Week 52	Week 52	n	216	215	431
		ADA negative, n (%)	156 (72.2)	148 (68.8)	304 (70.5)
		ADA induced, n (%)	56 (25.9)	65 (30.2)	121 (28.1)
		ADA boosted, n (%)	0	1 (0.5)	1 (0.2)
		ADA positive without boosted, n (%)	2 (0.9)	1 (0.5)	3 (0.7)
		Missing[a], n (%)	2 (0.9)	0	2 (0.5)
NAb[b]	Baseline	n	2	2	4
		Positive, n (%)	0	0	0
		Negative, n (%)	2 (100)	2 (100)	4 (100)
		Proportion of NAb positive (%)[c]	0	0	0
	Week 4	n	8	6	14
		Positive, n (%)	8 (100)	6 (100)	14 (100)
		Negative, n (%)	0	0	0
		Proportion of NAb positive (%)[c]	3.7	2.8	3.3
	Week 8	n	45	50	95
		Positive, n (%)	45 (100)	50 (100)	95 (100)
		Negative, n (%)	0	0	0
		Proportion of NAb positive (%)[c]	21.1	23.4	22.2

Parameter	Visit	Statistics	ALT-L9 (N=216)	Eylea (N=215)	Overall (N=431)
	Week 16	n	5	7	12
		Positive, n (%)	4 (80.0)	7 (100)	11 (91.7)
		Negative, n (%)	1 (20.0)	0	1 (8.3)
		Proportion of NAb positive (%)[c]	1.9	3.3	2.6
	Week 32	n	8	7	15
		Positive, n (%)	7 (87.5)	5 (71.4)	12 (80.0)
		Negative, n (%)	1 (12.5)	2 (28.6)	3 (20.0)
		Proportion of NAb positive (%)[c]	3.4	2.4	2.9
	Week 52	n	16	24	40
		Positive, n (%)	16 (100)	24 (100)	40 (100)
		Negative, n (%)	0	0	0
		Proportion of NAb positive (%)[c]	7.9	11.9	9.9

Abbreviations: ADA, antidrug antibody; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; NAb, neutralizing antibody.
ADA status definitions: ADA negative = ADA status at baseline was "negative" or missing, at least 1 postbaseline ADA status was "negative", and there was no "positive" ADA status at all; ADA induced = ADA status at baseline was "negative" or missing, and at least 1 postbaseline ADA status was "positive"; ADA boosted = ADA status at baseline was "positive", and at least 1 postbaseline ADA titer value was higher compared with the baseline ADA titer value; ADA positive without boosted = ADA status at baseline was "positive", and all postbaseline ADA titer values were not higher compared with the baseline ADA titer value.
Note: Percentage was based on the number of subjects with available data at each visit.
a. ADA status at baseline was "negative" or missing, and there was no postbaseline ADA result at all.
b. NAb test was conducted exclusively when ADA positivity was confirmed.
c. The proportion was calculated based on the number of subjects with available ADA status at each visit.
Source: Table 14.2.5.1.1

Table 8. Summary of anti-drug antibody titre by visit (safety analysis set)

Visit	Statistics	ALT-L9 (N=216)	Eylea (N=215)	Overall (N=431)
Baseline	n	2	2	4
	<10, n (%)	0	1 (50.0)	1 (25.0)
	10, n (%)	2 (100)	1 (50.0)	3 (75.0)
	20, n (%)	0	0	0
	40, n (%)	0	0	0
Week 4	n	8	6	14
	<10, n (%)	3 (37.5)	3 (50.0)	6 (42.9)
	10, n (%)	5 (62.5)	3 (50.0)	8 (57.1)
	20, n (%)	0	0	0
	40, n (%)	0	0	0
Week 8	n	45	50	95
	<10, n (%)	18 (40.0)	25 (50.0)	43 (45.3)
	10, n (%)	27 (60.0)	24 (48.0)	51 (53.7)
	20, n (%)	0	1 (2.0)	1 (1.1)
	40, n (%)	0	0	0
Week 16	n	5	7	12
	<10, n (%)	2 (40.0)	4 (57.1)	6 (50.0)
	10, n (%)	3 (60.0)	3 (42.9)	6 (50.0)
	20, n (%)	0	0	0
	40, n (%)	0	0	0
Week 32	n	8	7	15
	<10, n (%)	1 (12.5)	3 (42.9)	4 (26.7)
	10, n (%)	7 (87.5)	2 (28.6)	9 (60.0)
	20, n (%)	0	1 (14.3)	1 (6.7)
	40, n (%)	0	1 (14.3)	1 (6.7)
Week 52	n	16	24	40
	<10, n (%)	4 (25.0)	5 (20.8)	9 (22.5)
	10, n (%)	8 (50.0)	18 (75.0)	26 (65.0)
	20, n (%)	4 (25.0)	1 (4.2)	5 (12.5)
	40, n (%)	0	0	0

Abbreviations: N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data.
Note: Percentage was based on the number of subjects with available data at each visit.
Source: Table 14.2.5.1.1

The applicant presented summarised sub-group analyses for TEAEs by SOC and PT, by ADA status, and SAEs by SOC and PT, by ADA status for the SAF in the final CSR.

ALT-L9-01

Immunogenicity was assessed by measuring [anti-drug antibody (anti-ALT-L9 antibody]] before the first dose of the IP and at Week 12 after administration.

The immunogenicity analysis showed that both the study group and the control group were negative at baseline (prior to the first dose of the IP) and Week 12:

Table 9. Immunogenicity analysis

	Study group (N=14)	Control group (N=14)	Total (N=28)	p-value
Baseline (Pre-dose), N (%)				-
Positive	0 (0.00)	0 (0.00)	0 (0.00)	
Negative	14 (100.00)	14 (100.00)	28 (100.00)	
Week 12, N (%)				-
Positive	0 (0.00)	0 (0.00)	0 (0.00)	
Negative	13 (100.00)	14 (100.00)	27 (100.00)	

Note 1) N (%) : Number of subjects (percentage); the percentage was calculated by group

Note 2) Subject [redacted] was excluded from the analysis for tests not performed at Visit 6 (Week 12), and no AEs occurred in the subject.

Treatment group: Study group = ALT-L9, Control group = Eylea injection

-: Not analyzed

Report Generated by Program: Table 74. Immunogenicity assessment [anti-drug antibody (anti-ALT-L9 antibody)] before the first dose of the IP and at Week 12 after IP administration (Safety set).sas

2.4.3. Discussion on clinical pharmacology

Pharmacokinetic data analysis

For Study ALT-09-01, the methods described for analysis, or the PK data are overall acceptable. As systemic absorption of aflibercept is limited, the applicant is not required to show that the results comply with the typical bioequivalence guidelines. A t-test to compare the PK parameters for statistical significance is acceptable for analysis.

For Study ALT-09-03, the proposed summary statistics (arithmetic and geometric mean, standard deviation [SD], coefficient of variation [CV%], minimum [min.], maximum [max.], and median) are acceptable. In the initial scientific advice (EMA/SA/0000063713), it was advised that the 95% confidence intervals of the difference in PK summary measures should also be provided, and that success criteria should be pre-specified in the protocol. Although the analysis and success criteria were detailed in the study protocol, the 95% CIs for the difference could not be found in the study report, and it was unclear whether the success criteria for PK similarity were met. However, the issue can be considered solved on the basis of the overall data provided.

Pharmacokinetics in the target population

Based on current evidence it is agreed that it is unlikely that the systemic concentration of aflibercept after intravitreal injections would be high enough to exert a clinically relevant systemic effect. Therefore, it was agreed that a dedicated study to demonstrate PK similarity assessment between ALT-L9 and RefMP in healthy subjects is not needed.

However, whether systemic exposure levels are within a similar range as for the reference product will need to be adequately shown also for the proposed biosimilar ALT-L9 by providing adequate PK data.

Study ALT-L9-01

Study ALT-L9-01 is a Phase 1 study to evaluate safety, efficacy, and PK of ALT-L9 in patients with neovascular (wet) age-related macular degeneration. The PK objective was to evaluate and compare the systemic PK of ALT-L9 (aflibercept) to the marketed product Eylea. Overall, the design of the design of this study was acceptable to support the PK objective.

On the protocol it is established that all subjects participating in this study will have a wash-out at least 8 weeks from the last administration of anti-VEGF drug to baseline at which the first IP is taken, in order to remove the efficacy of the anti-VEGF drug administered prior to participation in this study. However, 5 subjects per treatment group showed plasma concentration of aflibercept at pre-dose.

Therefore, the applicant provided two tables with the calculated baseline plasma concentration-time data of aflibercept for these subjects in the Eylea group and ALT-L9 group with plasma concentrations obtained using the superposition principle and adjusted the plasma concentration data at the corresponding time points of measurement.

It is clear from the data in the PK report that the mean plasma concentrations for the test (ALT-L9) were notably higher than the reference (Eylea) at all time-points and importantly were substantially higher for the earliest time-points at 0.125 days and 1 day (T_{max}). This higher exposure is reflected in the exposure PK parameters (C_{max}, $AUC_{0\text{-}28d}$, and $AUC_{infinity}$), where the geometric means for ALT-L9 are substantially higher than in Eylea.

This was noted in the initial scientific advice received by the applicant, and the applicant was advised to provide a root cause analysis for this difference. The applicant has detailed that the higher geometric mean PK exposures were likely caused by a single subject in the ALT-L9 group. When this subject was excluded from the PK analysis, the exposure parameters geometric means for the exposure parameters for the ALT-L9 were reduced and were more similar to the Eylea parameters. It is however noted that the exposure parameters are still overall higher.

The other PK parameters (C_{max}, C_{last}, $T_{1/2}$, CL/F, and V_d/F) are overall similar. It was noted by the applicant that the $T_{1/2}$ is higher than anticipated and attributes this to the sparse PK sampling. This is overall acceptable.

An independent t-test was used to compare the PK parameters between each group, and it was demonstrated that there was no statistically significant difference found between the two groups for all parameters. It is noted however, that the statistical analysis was performed on the full PK analysis set, as opposed to the set that excluded the outlier subject. As there is still a notable difference for the exposure parameters between the test and reference groups with the subject excluded, the applicant repeated the t-test analysis and confirmed that the there is no statistically significant difference in exposures between the test and reference with the outlier subject excluded**.**

Given that the above concerns are addressed, the results of this study are overall supportive of PK similarity between the test (ALT-L9) and reference (Eylea) products following an intra-vitreal injection.

ALT-L9-03

Study ALT-L9-03 is a Phase 3 study to evaluate efficacy, and safety of ALT-L9 in patients with neovascular (wet) age-related macular degeneration, with evaluation of the systemic PK as a secondary objective. Overall, the study design is acceptable for the PK objective.

It is established in inclusion criteria nº 4 of the protocol that individual must be newly diagnosed, treatment-naïve, active subfoveal or juxtafoveal CNV lesion secondary to AMD in the study eye and in exclusion criteria nº 2 it is established that individuals with any previous IVT anti-VEGF treatment (e.g., bevacizumab, aflibercept, ranibizumab, or brolucizumab) in the study eye would be ineligible to participate in this study. However, in the Eylea group there is a subject with plasma concentration of aflibercept in the baseline. After a further investigation of any potential causes directly related to the subject that might explain the quantifiable concentration, no conclusive explanation has been identified. This investigation provided further support that there are no important technical errors, protocol deviations or other notable information relevant to this subject but no justification of this issue was provided. The overall study design is otherwise acceptable for the PK objective.

The PK subset consisted of a subset of subjects who volunteered to provide samples for PK analysis. The PK set consisted of 25 subjects for the test and 21 subjects for the reference. The sample size of the PK set has been adequately justified. It was recommended in the initial scientific advice that patients in the PK subset would be comparable in terms of all known variables that may affect the pharmacokinetics of the active substance. It can be accepted that the population demographics were mostly similar between the test and reference groups.

From Figure 7 and Table 31 it is noticeable that there was a notable difference between the test and reference groups at Day 2 (24 hours after the first dose), and similar concentrations at Week 8 + 1 day. When split by geographic region it is shown that, for the European region, the geometric mean plasma concentration 24-hour post-dose of aflibercept on Day 2 and Day 58 were similar between treatments for the European region. However, in the Asia Pacific region, aflibercept plasma concentrations observed were higher for Eylea group compared to ALT-L9 group. Due to the low sample size and the high variability no conclusion can be made.

Aflibercept plasma concentrations for the PK set summarised by ADA status were also presented in the study report. Only 3 of the 25 subjects in the ALT-L9 group showed positive ADA status up to Week 8, and all were positive for NAbs. There was a notable difference in the geometric mean plasma concentrations between the ADA negative subjects (52.0 ng/mL) when compared with the ADA induced (41.7 ng/mL) and ADA positive without boosted (33.4 ng/mL) groups. However, given the low incidence of ADAs in the test group these results should be interpreted with caution. Additionally, as there was no incidence of ADAs in the reference group up to Week 8, so no meaningful comparison between the test and reference products can be drawn.

Overall, it can be accepted that free aflibercept plasma concentrations between the test (ALT-L9) and reference (Eylea) groups were similar after the first (Day 2) and third (Week 8 + 1 Day) doses in Study ALT-L9-03.

Immunological events

In **Study ALT-L9-01**, immunogenicity analysis showed that subjects in both treatment arms had negative results for ADAs at both time points where the assessment was performed, baseline (prior to the first dose of the study treatment) and Week 12. As some issues are identified with the method validation this analysis is considered as supportive only (refer to Clinical section above).

In **Study ALT-L9-03**, full immunogenicity data through Week 52 of the study was provided in the final CSR.

At baseline, anti-drug antibody (ADA) status was positive for 2 subjects each in both the treatment groups. Overall, the proportion of subjects with ADA-induced or ADA-boosted and positive neutralising antibodies (NAbs) were comparable between the treatment groups. Of the ADA-positive subjects, the proportion of subjects with positive NAbs was >70% in both treatment groups at every visit except for the baseline visit.

In the ALT-L9 (aflibercept) group, an ADA titre of 20 was reported in 4 subjects at Week 52. In the Eylea group, an ADA titre of 20 was reported in 1 subject each at Weeks 8, 32, and 52, and ADA titre of 40 was reported in 1 subject at Week 32. All other subjects had titres of ≤10.

The applicant provided additional discussion on the higher observed incidence of ADA positivity (not generally in line with that expected for aflibercept) at Week 8 in both treatment arms, highlighting further that, from an immunogenicity perspective, there were no notable differences between the two treatment groups throughout the study, and confirming that no increase in immune-mediated TEAEs was observed. The applicant's response was accepted.

Impact of immunogenicity on efficacy

A subgroup analysis for the primary endpoint by ADA status (ADA negative, ADA induced, ADA boosted, and ADA positive without boosted), at Weeks 8, 32 and 52, was performed. Subgroup analysis results for ADA negative and ADA induced were consistent with the results of the primary efficacy endpoint in the overall population.

Impact of immunogenicity on safety

No correlation was observed between ADA positive status or NAb status and the occurrence of immune-mediated TEAEs, including ISRs. There were no cases of immune-mediated TEAEs in subjects with ADA-positive status in either treatment groups throughout the trial.

For the purpose of evaluation of immunogenicity for ALT-L9, the applicant provided adequate justification for how the findings from Study ALT-L9-03, conducted in the nAMD population, may be extrapolated to younger target populations in the other claimed indications.

Overall, from an immunogenicity perspective, in line with the known immunogenicity profile of Eylea, the incidence of patients with ADA positive status was low for ALT-L9. Titres were also low. The immunogenicity profiles of both treatment arms are considered comparable.

2.4.4. Conclusions on clinical pharmacology

An acceptable level of PK similarity was demonstrated between ALT-L9 and Eylea. The immunogenicity profiles of ALT-L9 and Eylea are considered comparable.

2.4.5. Clinical efficacy

Table 10. List of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Healthy Subjects or Diagnosis of Patients	Number of Subjects (Randomized)	Study Status; Type of Report
Efficacy, Safety, PK	ALT-L9-01	Module 5.3.5.1	To evaluate the safety, efficacy and PK characteristics of ALT-L9 following a total of 3 doses at 4-week intervals for 16 weeks in subjects with neovascular (wet) AMD	Phase 1, multicenter, double-masked, randomized, active-controlled, parallel-group study	ALT-L9 or EYLEA (2 mg) in the study eye by IVT injection once every 4 weeks for 8 weeks in the treatment period for a total of 3 doses Total duration (excluding screening): 16 weeks (treatment period: 8 weeks, follow-up period: 8 weeks)	Neovascular age-related macular degeneration (wet AMD)	28	Complete; Full
Efficacy, Safety, PK	ALT-L9-03	Module 5.3.5.1	To demonstrate that the biosimilar candidate ALT-L9 2 mg/50 µL is equivalent to Eylea (aflibercept), as well as to evaluate the safety, efficacy, systemic exposure, and immunogenicity of ALT-L9 compared with Eylea in subjects with neovascular (wet) AMD	Phase 3, multicenter, double-masked, randomized, active-controlled, parallel-group study	ALT-L9 or EYLEA (2 mg) in the study eye by IVT injection once every 4 weeks for 8 weeks and then once every 8 weeks for 40 weeks in the treatment period for a total of 8 doses Total duration (excluding screening): 52 weeks (treatment period: 48 weeks, follow-up period: 4 weeks)	Neovascular age-related macular degeneration (wet AMD)	431	Complete; Full

2.4.5.1. Dose response studies

Not applicable

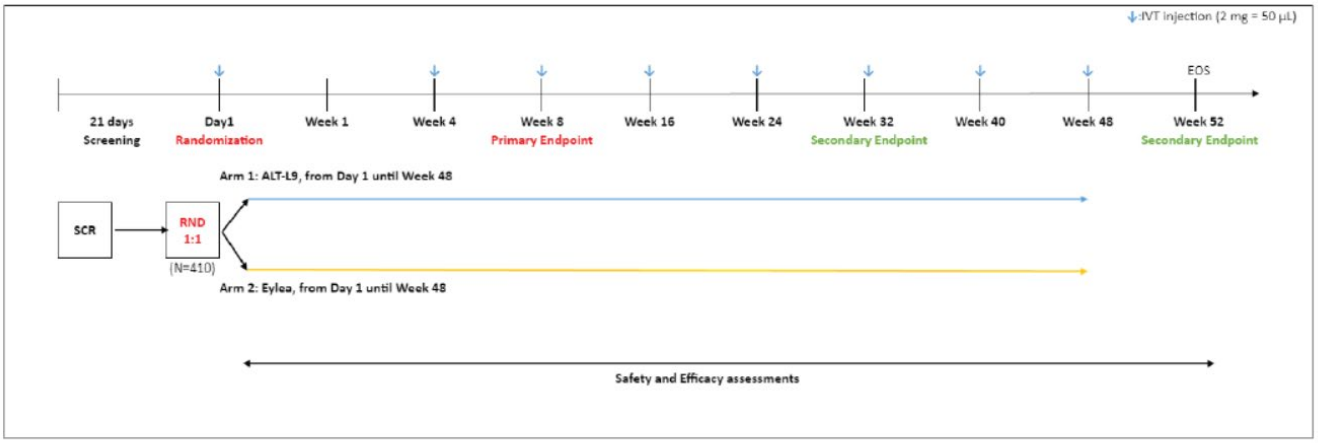
2.4.5.2. Main study

ALT-L9-03 A Randomised, Phase 3, Double-Masked, Parallel-Group, Multicentre Study to Compare the Efficacy and Safety of ALT-L9 Versus Eylea® in Patients With Neovascular Age-Related Macular Degeneration (ALTERA)

Study design

This phase 3, multicentre, double-masked, randomised, parallel-group clinical study evaluated ALT-L9 versus Eylea in subjects with nAMD. The study consists of 3 periods: a Screening Period (up to 21 days) to assess subjects' eligibility, the Treatment Period (baseline to Week 48), and a Follow-up Period (Week 48 to Week 52). Subjects visited the site at screening, baseline (Day 1), and Weeks 1, 4, 8, 16, 24, 32, 40, 48, and 52 (EOS Visit). Additional visits were needed for subjects who consented to have PK samples taken (the PK subpopulation) on Day 2 and Week 8 + 1 day. For each subject, study duration will be approximately 52 weeks, including follow-up.

Figure 2. Study design



Abbreviations: EOS, End-of-Study; IVT, intravitreal; RND, randomization; SCR, screening.

Study population

Subjects with nAMD, BCVA of 20/40 to 20/200 (both inclusive) in the study eye using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart (≤73 and ≥34 ETDRS letters) at screening and Day 1 before randomisation; total lesion area of ≤9.0 disc areas (≤22.86 mm^2) in size (including blood, scars, and neovascularisation) in the study eye; newly diagnosed, treatment-naive, active subfoveal or juxtafoveal CNV lesion secondary to age-related macular degeneration (AMD) in the study eye, the area of CNV ≥50% of the total lesion area in the study eye.

Randomisation and blinding

On Day 1 (baseline visit), all eligible subjects were randomly assigned (using a permuted block design) in a 1:1 ratio to either ALT-L9 or Eylea for the duration of the Treatment Period, stratified by geographic region where the subject was enrolled (Europe vs Asia Pacific), BCVA ETDRS letter count recorded at baseline (<64 letters vs ≥64 letters), and CST at screening (<300 microns vs ≥300 microns).

On confirmation of eligibility for a given subject to participate in the study, a unique randomisation number for that subject was assigned via an IRT. The IRT was accessed immediately by study site personnel after confirmation of the subject's eligibility had been recorded. 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. The randomisation number for a given subject is used to identify the study drug that will be administered to that subject and is not assigned to any other subject.

ALT-L9 is provided in vials and Eylea is supplied to the study sites in a PFS for administration to the individual subjects. The study treatments were labelled in a masked manner. Because of the different presentation of the 2 study drugs, the external packages were designed to look identical; however, to ensure masking is maintained, the study drug preparation and administration is done by the unmasked site staff. The study drug injections are administered by the designated unmasked site staff in such a manner that the subjects remain masked. Masked staff or any other study personnel are not involved in any activities pertaining to preparation or administration of the study drug. All study drug documentation (i.e., study drug preparation documents or any injection-related records) are maintained only by unmasked site staff.

Description of trial intervention

Table 11. Details of study treatments

	Preparations to be Administered	
	ALT-L9	Eylea
Manufacturer	[redacted]	
Active ingredient	Aflibercept	Aflibercept
Dosage	Single dose once every 4 weeks until Week 8 and once every 8 weeks until Week 48	Single dose once every 4 weeks until Week 8 and once every 8 weeks until Week 48
Route	Ophthalmic IVT injection	Ophthalmic IVT injection
Formulation	Single use vial, used only for the treatment of a single eye (ie, the study eye)	Single prefilled syringe to be used only for the treatment of a single eye (ie, the study eye).
Batch number(s)	[redacted]	

Abbreviations: EU, European Union; IVT, intravitreal; QP, qualified person.

Concomitant and rescue therapies

All medications and other treatments taken by the subject during the study, including those treatments initiated before the screening for the study, are recorded on the eCRF. The standard of care or other approved treatment practice for nAMD according to the investigator in the fellow eye is permitted and is recorded in the appropriate eCRF page.

Medications taken by or administered to the subject within 30 days of screening are recorded in the eCRF. After the baseline visit, medication to treat minor treatment-emergent illness(es) is generally permitted; however, the following therapies are expressly prohibited throughout the study:

- Intraocular corticosteroids in the study eye
- Periocular corticosteroids in the study eye
- Laser treatment in the study eye
- Any anti-VEGF treatment other than study treatment in the study eye
- Systemic corticosteroids except short-term (<14 consecutive days) oral corticosteroids (inhaled, nasal, intra-articular, and dermal corticosteroids are not considered systemic and are allowable)
- Systemic anti-VEGF therapy
- Any investigational drug or device in either eye or systemically

Study assessments

Best-corrected Visual Acuity Measured Using Early Treatment Diabetic Retinopathy Study Standards

ETDRS visual acuity testing precedes any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Visual acuity of the study eye is assessed at each study visit and the fellow eye is assessed at the Screening and EOS Visits only, using BCVA (best correction determined from protocol refraction). BCVA is assessed by a qualified BCVA assessor masked to the study treatment assignment. BCVA is measured in a sitting position using ETDRS-like visual acuity testing charts. BCVA is reported as ETDRS letter score. ETDRS chart series used during the study included ETDRS original series, European Wide Series (3,1,2), and 2702 Number Series. The chart series was selected based on the country of the site. All ETDRS chart series were validated and consistently used throughout the study. Also, the same chart series was consistently used for a subject throughout the duration of the study.

Central Subfield Thickness and Intraretinal or Subretinal Fluid Measured by Spectral Domain-Optical Coherence Tomography

SD-OCT was used at screening for both eyes. At all other scheduled visits, the SD-OCT is conducted in the study eye only, and SD-OCT was not performed on the Day 2 and on the Week 8 (+1 day) visits for the PK subpopulation. These assessments are performed by a trained technician or investigator at the sites after BCVA assessment and before any study drug administration. The SD-OCT machine used for an individual subject will not change for the duration of the study. CST and CFT are measured by SD-OCT. The CST represents the average retinal thickness within a 1-mm diameter area around the foveolar centre point from retinal pigment epithelium to internal limiting membrane, inclusively. The CFT represents the retinal thickness at the foveolar centre point. All SD-OCT images are obtained by trained and study-certified site personnel at the study site and forwarded to the CRC for independent standardised analysis and storage. Note: Although SD-OCT is the preferred method and is referred to throughout the protocol, other types of optical coherence tomography could be used, if agreed to and validated by the CRC, as specified in the applicable study manual.

Choroidal Neovascularisation Measured by Colour Fundus Photography and Fluorescein Angiography

CFP and FA are performed in the study eye at the screening, Week 32, and EOS Visits and in the fellow eye at the Screening Visit only. In case of early termination, CFP and FA are not repeated if there was a CFP and FA assessment within the previous 12 weeks. A standardised procedure for the collection of FA and CFP images was provided by the CRC in a separate manual. The equipment and examiners at each site were certified before evaluation of study subjects.

Objectives, endpoints and estimands

Primary Objective
The change from baseline in BCVA at Week 8 as measured by the ETDRS letter score.

BCVA is reported as the continuous ETDRS letter score (ranges from 0 to 100 letter scores). The change from baseline of BCVA at a post-baseline visit is a continuous parameter that measures the change in visual acuity. A positive change indicates an improvement and a negative change indicates a worsening. Additionally, the change from baseline of BCVA is grouped into categories of gain/loss of at least 5, 10, or 15 letters, where a positive change indicates a gain, and a negative change indicates a loss.

Secondary objectives

• Change from baseline in BCVA letter score in the study eye over time up to Week 52 using the ETDRS protocol

• Proportion of subjects with a loss of at least 5, 10, or 15 letters in BCVA letter score in the study eye over time up to Week 52, compared with baseline, using the ETDRS protocol

• Proportion of subjects with a gain of at least 5, 10, or 15 letters in BCVA letter score in the study eye over time up to Week 52, compared with baseline, using the ETDRS protocol

• Change from baseline in CST in the study eye over time up to Week 4 and Week 52, as measured by SD-OCT

• Proportion of subjects with existing intraretinal or subretinal fluid in the study eye over time up to Week 4 and Week 52, compared with baseline, as measured by SD-OCT

• Change from baseline in the total size of the CNV area in the study eye over time up to Week 52, as measured by FA.

• Proportion of subjects with active CNV leakage in the study eye over time up to Week 52, compared with baseline, as measured by FA

Planned analyses

- The Enrolled Set: consists of all individuals who signed the informed consent form, regardless of randomisation.
- The Intent-to-Treat (ITT) Set: consists of all randomised subjects, irrespective of any deviation from the protocol or premature discontinuation. Subjects are analysed under the treatment group as randomised. The ITT Set was used for the primary analyses of efficacy
- The Per-Protocol Set (PPS): consists of all randomised subjects with at least 1 baseline and post-baseline assessment of BCVA, and for whom there were no major protocol deviations affecting efficacy at Week 8. Subjects were analysed under the treatment group as randomised. The PPS is used for supportive analyses of efficacy.

The primary estimand for the primary efficacy endpoint was analysed using an analysis of covariance (ANCOVA) model to fit the change from baseline in BCVA at Week 8 on the ITT Set in each imputed dataset. The ANCOVA included treatment arms (ALT-L9 vs Eylea; reference Eylea), and the stratification factors included geographic region of enrolment (Europe vs Asia Pacific), baseline BCVA (<64 letters vs ≥64 letters), and screening CST (<300 microns vs ≥300 microns) used for the randomisation as fixed factors.

Equivalence was to be concluded for the Food and Drug Administration (FDA) if the 90% CI around the treatment difference at Week 8 was within the predefined equivalence margin of ±3.49 letters. Equivalence was concluded for the other agencies if the 95% CI at Week 8 was within the predefined equivalence margin of ±3.49 letters. The secondary and tertiary estimands for the primary efficacy endpoint were analysed in the same manner as the primary estimand for the primary efficacy endpoint.

Planned subgroup analyses

To assess the homogeneity of the treatment effect across various demographic and stratification factor subgroups, plus ADA and NAbs positivity as appropriate, exploratory sub-group analyses of the primary, secondary, and tertiary estimands of the primary efficacy endpoint were performed.

Sample size determination

To calculate an appropriate sample size for the study, a literature review was performed based on the following selection criteria: IVT aflibercept 2 mg every 2 months (8 weeks); active, subfoveal, CNV lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to AMD; change from baseline in BCVA ETDRS letter score as an endpoint; comparative treatment with sham injection where possible.

With an assumed SD of 9.5 for Eylea at Week 8, a true hypothesised treatment difference of 0, an alpha of 0.025 (i.e., a 2-sided 95% CI) for the European Medicines Agency (EMA), Ministry of Food and Drug Safety (MFDS), Pharmaceuticals and Medical Devices Agency (PMDA), and agencies other than the FDA, and an equivalence range for the difference in BCVA letters of ±3.49 letters, 194 evaluable subjects per treatment group (388 subjects total) were expected to provide approximately 90% power to ascertain the efficacy equivalence of ALT-L9 versus Eylea with respect to the primary endpoint. For the FDA, with an alpha level of 0.05 (i.e., implementing a 2-sided 90% CI) and retaining the same assumptions, the same sample size provided approximately 95% power. For the primary efficacy endpoint analysis at Week 8, a maximum dropout of 5% was assumed, also considering the requirements for the PPS analysis of the primary endpoint. After including a 5% dropout to Week 8, 205 subjects per treatment group (410 subjects total) were planned to be randomised. This sample size ensured a power of at least 80% for the supportive analysis of the primary endpoint on the PPS up to an exclusion rate of around 23% for the EMA/MFDS/PMDA analysis and up to an exclusion rate of around 37% for the FDA analysis. The sample size was calculated using the PASS 2020 (version 20.0.1) software.

Error probabilities, adjustment for multiplicity and interim analyses

No multiplicity adjustment was planned or required.

Two database locks (DBLs) are planned for this study: at the time of primary analysis (interim analysis, i.e., the analysis presented in this CSR) and the other at the time of Week 52/EOS analysis. The study team remained masked to the study treatments until the final analysis. The unmasked analyses for the primary analysis (interim analysis) timepoint for this CSR were conducted by a separate analysis team.

Changes from protocol-specified analyses

Table 12. Revision history

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	07-Jul-2023	[redacted]	Initial Released Version
2.0	04-Dec-2023	[redacted]	Main changes: 1. Sensitivity analyses were added for wrong-stratification, and BCVA=0 cases. 2. ICE6 and ICE7 were added. 3. Sub-group analysis for fellow eye treatment with anti-VEGF medications was added.

Data quality assurance

The Sponsor or its designee performs the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data. The Sponsor arranges audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits are independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures are performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

Changes in the planned conduct of the study

The original protocol dated 15 Nov 2021 was amended to Protocol version 2.0, dated 28 Sep 2022. Changes incorporated in this amendment included some clarifications and updates to the protocol, including the secondary endpoints, study design, eligibility criteria, sample size, and Schedule of Assessments.

After data unmasking, a programming error was identified leading to remapping of immunogenicity assessments. Details are mentioned below:

• During review of outputs post unmasking on 05 Jan 2024, it was observed that for immunogenicity the EOT assessment for early study terminators was mapped to a full study schedule, rather than the study schedule for immunogenicity. In light of this, the mapping of EOT assessments for immunogenicity was updated to map these assessments to the latest applicable immunogenicity assessment.

Results

Participant flow and numbers analysed

Disposition of Subjects

During the study, 642 subjects were screened, of which 211 subjects were screen failures and 431 subjects were randomised (216 subjects in the ALT-L9 group and 215 subjects in the Eylea group). When 205 subjects had been randomised in each treatment group as planned per protocol, screening

was closed. There were a small number of subjects still undergoing screening; these subjects completed the Screening Period (21 days) and were allowed to continue, resulting in a slightly higher number of subjects randomised than originally planned. Overall, 24 (5.6%) subjects discontinued the study treatment, and 26 (6.0%) subjects discontinued the study. The difference between 24 and 26 is due to 2 subjects:

- One subject (ALT-L9 group) experienced an AE of ischaemic stroke after the last dosing at Week 48 and discontinued the study thereafter.
- One subject (Eylea group) withdrew consent after the last dosing at Week 48.

The proportion of subjects who discontinued the study treatment and/or the study were comparable between the treatment groups, and the rate of discontinuation was generally in line with that expected at the start of the study (5% as stated in the protocol).

The proportion of subjects who discontinued the study drug and/or the study due to AEs was higher in the Eylea group compared with the ALT-L9 group.

Protocol Deviations

Major protocol deviations were reported in 109 (25.3%) subjects. The proportion of subjects who reported major deviations were comparable between the treatment groups. The most common major protocol deviation category was "study procedure/other", reported in 17 (7.9%) subjects in the ALT-L9 group and 28 (13.0%) subjects in the Eylea group.

Those subjects in receipt of prohibited medications either regarded as protocol deviation or otherwise where the receipt was deemed to have had a possible effect on primary efficacy were then excluded from the PPS. Medications with a start date after the Week 8 visit were not considered as protocol deviations leading to PPS exclusion as they did not impact the primary efficacy measure. The use of prohibited medication leading to major protocol deviation was low (9 subjects total, 2.1%); while the use of these medications leading to major protocol deviation was higher in the ALT-L9 group compared with the Eylea group. There was no correlation found between the use of prohibited medication and perceived efficacy of the study treatment.

Data Sets Analysed

All enrolled subjects were included in the ITT Set and the SAF. Overall, 22 (5.1%) subjects were excluded from the PPS. Other subjects with major protocol deviations were not excluded from the PPS because their major protocol deviations did not affect primary efficacy at Week 8. The most common reason for exclusion from the PPS was "study treatment administered out of ±7-day window at Week 4 affecting efficacy up to and including Week 8 in study eye", reported in 6 (1.4%) subjects overall. Of the 70 subjects who signed the PK consent form, 46 (65.7%) subjects were included in the PKS. The most common reason for exclusion from the PKS was "screen failure", reported in 21 (30.0%) subjects, overall. Three out of the 24 subjects who were excluded from the PKS were randomised and treated, but subsequently had no PK sample collected at any stage.

Baseline data

Demographics and Baseline Characteristics

Demographic and baseline characteristics were comparable between the treatment groups.

Overall, mean (SD) age of the subjects was 74.2 (7.90) years; there was a higher proportion of females (59.9%); the most common race was White (83.3% of subjects); and all subjects belonged to

the 'Not Hispanic or Latino' ethnicity. Most subjects were from Europe (83.3%) compared with Asia Pacific (16.7%). Overall, 33 (7.7%) subjects were enrolled in Japan, according to the plan per the protocol.

At baseline, most (97.4%) subjects were not receiving treatment for the fellow eye. At baseline, a higher proportion of subjects had BCVA <64 letters (57.3%) compared with BCVA ≥64 letters (42.7%) and a higher proportion of subjects had CST ≥300 microns (64.5%) compared with CST <300 microns (35.5%).

Medical History

Ocular and non-ocular medical history reported was comparable between the treatment groups. Ongoing ocular history was reported for all subjects at baseline. Neovascular age-related macular degeneration is the disease under study and was the most common ongoing ocular history reported for all subjects, followed by dry age-related macular degeneration and cataract.

Any prior or concomitant ocular intervention was reported in 175 (40.6%) subjects, the most common intervention was cataract operation, reported in 154 (35.7%) subjects.

Ongoing non-ocular medical history at baseline was reported in 418 (97.0%) subjects, the most common non-ocular medical history was hypertension, reported in 275 (63.8%) subjects.

Prior Medications

Usage of prior medications was comparable between the treatment groups. Prior medications were used in 159 (36.9%) subjects. The most common prior medication was fluorescein sodium, reported in 66 (15.3%) subjects.

Concomitant Medications

Concomitant medications started before and continuing through the first administration of study treatment on the study eye were reported in all subjects during the study and concomitant medications that started on or after the first administration of the study treatment on the study eye were reported in 421 (97.7%) subjects. Overall, the proportion of subjects taking any concomitant medications was comparable between the treatment groups. The most common concomitant medication that started before the first administration of the study drug on the study eye was tropicamide, reported in 290 (67.3%) subjects. The most common concomitant medication that started on or after the first administration of the study drug on the study eye was povidone-iodine, reported in 324 (75.2%) subjects.

Overall, 4 (1.9%) subjects in the ALT-L9 group and 2 (0.9%) subjects in the Eylea group received subsequent medications on the study eye. The most common subsequent medication on the study eye was vancomycin which was reported in 3 subjects overall.

Measurements of Treatment Compliance

Qualified personnel administered the study drug in the study eye as an IVT injection. Compliance was monitored. Overall, compliance with the study drug was high for both treatment groups. All subjects who were assigned the study drugs received the study drug except for 1 subject at Week 24.

Details regarding the subject who was assigned the study drug but not administered are:

- The study drug was not administered to 1 subject in the ALT-L9 group at Visit 9 (Week 24) because of an AE of conjunctivitis. The subject resumed the study drug at Week 32.

The study drug was administered out of a ±7-day window at Week 4 for 5 subjects in the ALT-L9 group and for 3 subjects in the Eylea group; all 8 subjects were excluded from the PPS.

Extent of Exposure

The extent of exposure was similar between the treatment groups. The mean duration of exposure was 46.8 weeks for the ALT-L9 and 46.7 weeks for the Eylea group; the mean total number of doses administered was 7.8 for both the ALT-L9 group and the Eylea group. The mean extent of exposure was 99.7%, overall.

Outcomes and estimation

Primary Efficacy Endpoint

Overall, the proportion of ICEs affecting the Week 8 assessment for subjects in the ITT Set were comparable between the treatment groups. Any ICE was reported for 31 (14.4%) subjects in the ALT-L9 group and for 26 (12.1%) subjects in the Eylea group. The most common ICE was prohibited medication used, reported in 25 (11.6%) subjects in the ALT-L9 group and for 21 (9.8%) subjects in the Eylea group; ICEs of premature discontinuation of study treatment because of a reason other than LoE and study treatment administration outside of the ±7-day window were reported in <3% of subjects overall; other ICEs were not reported. For the consideration of the ICE related to prohibited medication used (ICE7), any medications falling under the relevant ATC4 codes that were deemed to be prohibited were classed as an ICE if starting at any point postbaseline before or on the visit of efficacy assessment. Thus, the consideration of prohibited medication use as an ICE is more widely applied than the instances leading to protocol deviation and/or PPS exclusion.

A high-level summary of the estimand handling approaches is provided as follows:

- The primary estimand is aligned with a treatment policy approach for all ICEs except death or discontinuation because of LoE (composite variable strategy).

- The secondary estimand allows for the assessment of the treatment effect in an alternative, hypothetical setting where all subjects take the assigned study treatment without interruption or early/late administration.

- The tertiary estimand is aligned with a principal stratum strategy, whereby all subjects are dosed consistently with study treatment and have an evaluable BCVA assessment.

For the primary estimand, the least squares (LS) mean for adjusted change from baseline in BCVA at Week 8 was 5.771 in the ALT-L9 (aflibercept) group and 7.863 in the Eylea group. The LS mean difference between treatments was -2.092 (standard error [SE]: 0.6834) (90% confidence interval [CI]: -3.216, -0.968; 95% CI: -3.431, -0.753). As the 90% CI and the 95% CI were contained entirely

within the predefined margin of ±3.49 letters, equivalence of the treatments was established for 95% CI for EMA, MFDS, PMDA, and other agencies, and 90% CI for the US FDA.

Results from analysis of the secondary and tertiary estimands were similar to those of the primary estimand, consistently demonstrating equivalence of the 2 treatments within the predefined margin of ±3.49 letters.

Sensitivity Analysis for Change from Baseline in BCVA at Week 8

Results from the following sensitivity analyses were supportive of the primary efficacy analysis:

- Change from baseline in BCVA of the study eye at Week 8 imputed per LOCF method for the ITT Set. For the primary estimand, the 90% CI was −3.324, −1.078 and the 95% CI was −3.540, −0.862; for the secondary estimand, the 90% CI was −3.009, −0.660 and the 95% CI was −3.235, −0.434.

- Change from baseline in BCVA of the study eye at Week 8 assessed using MMRM for the ITT Set. For the primary estimand, the 90% CI was −3.208, −0.951 and the 95% CI was −3.425, −0.734; for the secondary estimand, the 90% CI was −2.858, −0.459 and the 95% CI was −3.089, −0.228.

- Change from baseline in BCVA of the study eye at Week 8 for the PPS. For the primary estimand, the 90% CI was −3.110, −0.802 and the 95% CI was −3.331, −0.581; for the primary estimand with LOCF method, the 90% CI was −3.139, −0.830 and the 95% CI was −3.362, −0.608; for the secondary estimand, the 90% CI was −2.922, −0.544 and the 95% CI was −3.149, −0.316; and for the tertiary estimand, the 90% CI was −3.105, −0.794 and the 95% CI was −3.328, −0.571.

- Change from baseline in BCVA of the study eye at Week 8 with correct reading of stratification factor for the ITT Set. For the primary estimand, the 90% CI was −3.215, −0.971 and the 95% CI was −3.430, −0.756.
- Change from baseline in BCVA of the study eye at Week 8 with correct reading of stratification factor for the PPS. For the primary estimand, the 90% CI was −3.100, −0.795 and the 95% CI was −3.321, −0.574.

A tipping point analysis was performed as a sensitivity analysis for the change from baseline in BCVA of the study eye at Week 8 for the ITT Set.

As equivalence was observed in the analysis of the primary estimand, a 2-dimensional tipping point analysis was conducted based on the different levels of delta shift for the imputation in each treatment group, gradually increasing the severity of imputation involved for the ALT-L9 and/or Eylea treatment. The range of shifts was further increased compared with the CSR for primary analysis. Results showed that for a shift of up to 14 letters in favour of Eylea with no shift for ALT-L9, both the 90% and 95% CIs were contained entirely within the predefined margin; a tip occurred at a shift of 15 letters in favour of Eylea when the ALT-L9 group was unchanged. When a shift of 10 letters or more occurred in the ALT-L9 group, the 90% and 95% CIs were contained entirely within the predefined margin up to a maximum shift of 16 letters in the Eylea arm. These results indicate that the assumptions of data handling for the primary estimand of the primary efficacy endpoint are robust, and the robustness is further increased by increasing the range of shifts. The tipping point sensitivity analyses support the

findings of the primary efficacy analyses and confirm that the handling of missing data as MAR under treatment policy approach is appropriate, and major changes to these assumptions would not change the conclusion of equivalence between ALT-L9 and Eylea.

Sub-group Analysis for Change from Baseline in BCVA at Week 8

For the primary efficacy endpoint, the following subgroup analyses were performed for the ITT Set for the 3 defined estimands:

- ADA status (ADA negative, ADA induced, ADA boosted, and ADA positive without boosted) subgroups (at Weeks 8, 32, and 52)

- Baseline characteristics subgroups: Sex (male versus female); age category (<75 years versus ≥75 years); geographic region (Europe versus Asia Pacific); race (White versus Black or African American versus Asian versus American Indian or Alaska Native versus Native Hawaiian or Other Pacific Islander); ethnicity (Hispanic or Latino versus not Hispanic or Latino); baseline BCVA using the ETDRS protocol; screening CST as measured by SD-OCT; baseline lesion type as measured by FA; baseline CNV lesion size (presented with CNV area and CNV lesion area); baseline CNV area; baseline fluid status as measured by SD-OCT

- Fellow eye treatment with anti-VEGF medication status subgroups (up to Week 8, up to Week 32, and up to Week 52)

Overall, subgroup analysis results were supportive of the primary efficacy endpoint results. For the subgroup analysis of the geographic region of Europe (with >80% subjects overall), results were in line with the primary efficacy results. For the primary estimand, the LSM difference between treatments was −1.382 (SE: 0.7443) (90% CI, −2.607, −0.158; 95% CI, −2.841, 0.076); for the secondary estimand, the LSM difference between treatments was −1.197 (SE: 0.7885) (90% CI, −2.494, 0.100; 95% CI, −2.743, 0.349); and for the tertiary estimand, the LSM difference between treatments was −1.367 (SE: 0.7446) (90% CI, −2.595, −0.140; 95% CI, −2.831, 0.097). The 90% CI and the 95% CI for the Europe region were contained entirely within the predefined margin of ±3.49 letters and were narrower than that of the overall population, while the 90% CI and the 95% CI for the Asia Pacific region was outside of the predefined margin of ±3.49 letters. The equivalence margin and power for the study were determined based on application to the global population, and not for any specific regional subgroups. No specific regional differences in efficacy of note were observed, all CIs overlapped, and consistent trends in efficacy with respect to BCVA were noted at Week 8.

Secondary Efficacy Endpoints

The proportion of ICEs affecting assessments other than Week 8 was comparable between the treatment groups. The most common ICEs (reported in >10% of the subjects in either group at any visit) included prohibited medication used and study treatment administration outside of the ±7-day window in both the treatment groups. One subject in the ALT-L9 group died due to severe glioma during the study; this death was defined under the criteria of ICE1 and led to no data being able to be collected at the Week 48 and Week 52 assessments. No subjects discontinued the study treatment because of LoE during the study. One subject in the ALT-L9 group received incorrect administration of the study treatment (Eylea) at Week 32, thus affecting the Week 32, 40, 48, and 52 assessments.

Change from Baseline in BCVA Letter Score in the Study Eye Over Time up to Week 52 Using the ETDRS Protocol

One of the secondary efficacy endpoints was change from baseline in BCVA letter score in the study eye over time up to Week 52 using the ETDRS protocol. The same estimands (primary, secondary, and tertiary) as for the primary efficacy endpoint were repeated for each visit up to Week 52.

Subjects in both treatment groups responded well to treatment over the study based on the observed improvements in visual acuity. Progressive increases in the change from baseline in mean BCVA letter score were observed in both treatment groups. While there were slightly higher mean BCVA letter scores observed in the Eylea group, the mean responses were comparable (less than 4 letters, and mainly within 1 to 2 letters) during the study.

For the primary estimand, the LSM difference (SE) was −0.866 (0.6169), −1.027 (0.7685), −0.589 (0.9339), −1.309 (0.8539), −1.264 (0.9003), −2.936 (0.9457), and −1.944 (0.9373) at Week 4, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52, respectively. The results from analysis of the secondary and tertiary estimands were similar to those of the primary estimand. The results for the PPS were similar to results of the ITT Set. These results demonstrated comparability between the 2 treatment groups.

Results from the sensitivity analysis performed for the endpoint were in line with the primary estimand results. The 90% and 95% CIs for the sensitivity analyses were generally comparable.

Proportion of Subjects with a Loss of At Least 5, 10, or 15 Letters in BCVA Letter Score in the Study Eye Over Time up to Week 52, Compared With Baseline, Using the ETDRS Protocol

Overall, the adjusted proportion of subjects with a loss of at least 5, 10, or 15 letters in BCVA was low in both treatment groups. At Week 52, the adjusted proportion of subjects with a loss of at least 5, 10, or 15 letters in the Eylea group was lower than in the ALT-L9 group.

In the ALT-L9 group, the adjusted proportion of subjects with a loss of at least 5 letters fluctuated over time, with a trend of increase from Week 4 to Week 52. In the Eylea group, the adjusted proportion of subjects with a loss of at least 5 letters increased from Week 4 to Week 32, then decreased slightly by Week 52. Similar results were observed for adjusted proportion of subjects with a loss of at least 10 or 15 letters.

At Week 52, for the primary estimand, the adjusted proportion of subjects with a loss of

- at least 5 letters: 10.6% in the ALT-L9 group and 4.0% in the Eylea group,
- at least 10 letters: 6.4% in the ALT-L9 group and 2.0% in the Eylea group,
- at least 15 letters: 3.4% in the ALT-L9 group and 1.0% in the Eylea group.

Similar results were observed for the tertiary estimand at Week 52. For the secondary estimand, a smaller difference between treatment groups was observed across all 3 categories of letter loss, when the hypothetical strategy was implemented.

Proportion of Subjects with a Gain of At Least 5, 10, or 15 Letters in BCVA Letter Score in the Study Eye Over Time up to Week 52, Compared with Baseline, Using the ETDRS Protocol

Overall, the adjusted proportion of subjects who gained at least 5, 10, or 15 letters in BCVA was comparable between the treatment groups for the primary, secondary, and tertiary estimands.

In both treatment groups, the adjusted proportion of subjects with a gain of at least 5 letters fluctuated over time, with a trend of increase from Week 4 to Week 52. Similar results were observed for adjusted proportion of subjects with a gain of at least 10 and 15 letters.

At Week 52, for the primary estimand, the adjusted proportion of subjects with a gain of

- at least 5 letters: 68.8% in the ALT-L9 group and 72.9% in the Eylea group,
- at least 10 letters: 41.5% in the ALT-L9 group and 44.6% in the Eylea group,
- at least 15 letters: 19.2% in the ALT-L9 group and 21.8% in the Eylea group

Change From Baseline in CST in the Study Eye Over Time up to Week 4 and Week 52, as Measured by SD-OCT

The mean CST (microns) decreased at all time points postbaseline, with the highest reduction observed at Week 52 (change from baseline: −134.6 microns for the ALT-L9 group and −122.4 microns for the Eylea group). The mean change from baseline in CST was comparable between the treatment groups. For this endpoint, a greater reduction in CST was observed in the ALT-L9 group compared with the Eylea group at both Week 8 and Week 52, with a higher reduction at Week 8 (for the primary estimand, LSM difference [SE], −5.971 [7.5634] microns) compared with at Week 52 (for the primary estimand, LSM difference [SE], −4.742 [8.8080] microns). At Week 8 and Week 52, the 90% and 95% CIs for the treatment difference (for all estimands) were wide and contained zero.

Proportion of Subjects with Existing Intraretinal or Subretinal Fluid in the Study Eye Over Time up to Week 4 and Week 52, Compared with Baseline, as Measured by SD-OCT

At baseline, either intraretinal or subretinal fluid was observed for all subjects in the ITT Set. The proportion of subjects with intraretinal or subretinal fluid fluctuated over time, with a trend of decrease from baseline to Week 52 in both treatment groups.

The risk difference (SE) for intraretinal or subretinal fluid was comparable between the treatment groups at Week 8 and Week 52.

Change From Baseline in Total Size of CNV Area in the Study Eye Over Time up to Week 52, as Measured by FA

At baseline, CNV was observed for all subjects. At Week 52, the mean change in total size of the CNV area decreased from baseline for both treatment groups, and the reduction observed was comparable between the treatment groups. At Week 52, the mean adjusted change from baseline (SD) in total size of the CNV area in the study eye was −2.0332 (4.97819) in the ALT-L9 group and −2.2743 (4.83611) in the Eylea group for the primary estimand.

Similar results were observed for the PPS.

Proportion of Subjects with Active CNV Leakage in the Study Eye Over Time up to Week 52, Compared with Baseline, as Measured by FA

At baseline, active CNV leakage was observed for all subjects in the ITT Set; at Week 52, active CNV leakage was observed in 124 (57.4%) subjects in the ALT-L9 group and 106 (49.3%) subjects and the Eylea group.

At Week 52, the proportion of subjects with active CNV leakage (%) in the study eye was comparable between the treatment groups.

Similar results were observed for the PPS.

Efficacy table

Table 13 summarises the efficacy results from the main studies 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 13. Summary of efficacy for trial ALT-L9-03

Title: A Randomized, Phase 3, Double-Masked, Parallel-Group, Multicenter Study to Compare the Efficacy and Safety of ALT-L9 Versus Eylea® in Patients With Neovascular Age-Related Macular Degeneration (ALTERA)			
Study identifier	Protocol Number: ALT-L9-03 EudraCT Number: 2021-004530-11		
Design	Phase 3, multicenter, double-masked, randomized, parallel-group clinical study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks (treatment period: 48 weeks, follow-up period: 4 weeks) not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	Study group: ALT-L9		ALT-L9 (2 mg) in the study eye by IVT injection once every 4 weeks for 8 weeks and then once every 8 weeks for 40 weeks in the treatment period for a total of 8 doses. Number of subjects randomized: 216
	Control group: EYLEA		EYLEA (2 mg) in the study eye by IVT injection once every 4 weeks for 8 weeks and then once every 8 weeks for 40 weeks in the treatment period for a total of 8 doses. Number of subjects randomized: 215
Endpoints and definitions	Primary endpoint	PE	Change from baseline in BCVA at Week 8 as measured by the ETDRS letter score
	Secondary endpoint	SE1	Change from baseline in BCVA letter score in the study eye over time up to Week 52 using the ETDRS protocol
	Secondary endpoint	SE2	Proportion of subjects with a loss of at least 5, 10, or 15 letters in BCVA letter score in the study eye over time up to Week 52, compared with baseline, using the ETDRS protocol

	Secondary endpoint	SE3	Proportion of subjects with a gain of at least 5, 10, or 15 letters in BCVA letter score in the study eye over time up to Week 52, compared with baseline, using the ETDRS protocol
	Secondary endpoint	SE4	Change from baseline in CST in the study eye over time up to Week 4 and Week 52, as measured by SD-OCT
	Secondary endpoint	SE5	Proportion of subjects with existing intraretinal or subretinal fluid in the study eye over time up to Week 4 and Week 52, compared with baseline, as measured by SD-OCT
	Secondary endpoint	SE6	Change from baseline in the total size of the CNV area in the study eye over time up to Week 52, as measured by FA
	Secondary endpoint	SE7	Proportion of subjects with active CNV leakage in the study eye over time up to Week 52, compared with baseline, as measured by FA
Database lock	10 November 2023 (interim database lock) 17 April 2024 (final database lock)		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat Set: All randomized subjects, irrespective of any deviation from the protocol or premature discontinuation Week 8 for primary endpoint, Week 52 for secondary endpoints		
Descriptive statistics and estimate variability	Treatment group	ALT-L9	EYLEA
	Number of subjects	216	215
	PE LSM (SE) for the adjusted change from baseline for the primary estimand	5.771 (0.5821)	7.863 (0.5888)
	SE1 LSM (SE) for the adjusted change from baseline for the primary estimand at Week 52	7.315 (0.7871)	9.259 (0.8018)
	SE2 Adjusted proportion for the primary estimand at Week 52	≥5 letters: 10.6% ≥10 letters: 6.4% ≥15 letters: 3.4%	≥5 letters: 4.0% ≥10 letters: 2.0% ≥15 letters: 1.0%
	SE3 Adjusted proportion for the primary estimand at Week 52	≥5 letters: 68.8% ≥10 letters: 41.5% ≥15 letters: 19.2%	≥5 letters: 72.9% ≥10 letters: 44.6% ≥15 letters: 21.8%

	SE4 LSM (SE) for the adjusted change from baseline for the primary estimand at Week 52	-116.023 (7.4471)	-111.281 (7.5733)
	SE5 Adjusted proportion for the primary estimand at Week 52	39.7%	39.1%
	SE6 LSM (SE) for the adjusted change from baseline for the primary estimand at Week 52	-1.890 (0.4174)	-2.123 (0.4188)
	SE7 Adjusted proportion for the primary estimand at Week 52	61.7%	55.1%
Effect estimate per comparison	PE Primary estimand	Comparison groups	ALT-L9, EYLEA
		LSM Difference (SE)	-2.092 (0.6834)
		95% CI	-3.431, -0.753
		P-value	Not applicable
	SE1 Primary estimand, Week 52	Comparison groups	ALT-L9, EYLEA
		LSM Difference (SE)	-1.944 (0.9373)
		95% CI	-3.781, -0.107
		P-value	Not applicable

Title: A Randomized, Phase 3, Double-Masked, Parallel-Group, Multicenter Study to Compare the Efficacy and Safety of ALT-L9 Versus Eylea® in Patients With Neovascular Age-Related Macular Degeneration (ALTERA)			
Study identifier	Protocol Number: ALT-L9-03 EudraCT Number: 2021-004530-11		
	SE2 Primary estimand	Comparison groups	ALT-L9, EYLEA
		Risk Difference (SE)	≥5: 6.7 (2.53) ≥10: 4.4 (1.96) ≥15: 2.5 (1.43)
		95% CI	≥5: 1.8, 11.7 ≥10: 0.6, 8.3 ≥15: -0.3, 5.3
		P-value	Not applicable
	SE3 Primary estimand	Comparison groups	ALT-L9, EYLEA
		Risk Difference (SE)	≥5: -4.2 (4.52) ≥10: -3.3 (5.05) ≥15: -3.0 (3.93)
		95% CI	≥5: -13.1, 4.7 ≥10: -13.2, 6.6 ≥15: -10.7, 4.7
		P-value	Not applicable
	SE4 Primary estimand, Week 52	Comparison groups	ALT-L9, EYLEA
		LSM Difference (SE)	-4.742 (8.8080)
		95% CI	-22.006, 12.521
		P-value	Not applicable
	SE5 Primary estimand, Weeks 52	Comparison groups	ALT-L9, EYLEA
		Risk Difference (SE)	0.9 (4.78)
		95% CI	-8.5, 10.2
		P-value	Not applicable
	SE6 Primary estimand, Week 52	Comparison groups	ALT-L9, EYLEA
		LSM Difference (SE)	0.233 (0.4887)
		95% CI	-0.724, 1.191
		P-value	Not applicable
	SE7 Primary estimand, Week 52	Comparison groups	ALT-L9, EYLEA
		Risk Difference (SE)	6.7 (4.95)
		95% CI	-3.0, 16.4
		P-value	Not applicable
Analysis description	The primary estimand for the primary efficacy endpoint was analyzed		

Title: A Randomized, Phase 3, Double-Masked, Parallel-Group, Multicenter Study to Compare the Efficacy and Safety of ALT-L9 Versus Eylea® in Patients With Neovascular Age-Related Macular Degeneration (ALTERA)	
Study identifier	Protocol Number: ALT-L9-03 EudraCT Number: 2021-004530-11
	using an analysis of covariance (ANCOVA) model to fit the change from baseline in BCVA at Week 8 on the ITT Set in each imputed dataset. The ANCOVA included treatment groups (ALT-L9 versus Eylea), and the stratification factors included geographic region of enrollment (Europe versus Asia Pacific), baseline BCVA (<64 letters versus ≥64 letters), and screening CST (<300 microns versus ≥300 microns) used for the randomization as fixed factors. Equivalence was to be concluded for the EMA if the 95% CI around the treatment difference at Week 8 was within the predefined equivalence margin of ±3.49 letters. The secondary and tertiary estimands for the primary efficacy endpoint were analyzed in the same manner as the primary estimand for the primary efficacy endpoint.
	For the secondary efficacy endpoints, the descriptive summaries were presented as observed for each treatment group by each visit and listed. The same estimands (primary, secondary, and tertiary) as for the primary efficacy endpoint were applied, at all visits up to Week 52. Where ICEs relating to discontinuation or missed administration of the study treatment were assessed, dosing up to Week 48 was considered. All time points up to Week 52 were summarized descriptively for all efficacy measures based on the ITT Set.

2.4.5.3. Clinical studies in special populations

Not applicable

2.4.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.4.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.4.5.6. Supportive study

ALT-L9-01 - A Randomised, Double-masked, Active-controlled, Parallel-group, Phase 1 Study to Evaluate Safety, Efficacy and Pharmacokinetics of ALT-L9 in Patients with Neovascular (wet) Age-related Macular Degeneration

Study design

This clinical study was designed as a randomised, double-masked, active-controlled, parallel group, phase 1 study to evaluate the safety, efficacy, and PK characteristics of ALT-L9 following a total of 3 doses at 4-week intervals for 16 weeks (treatment period: 8 weeks, follow up period: 8 weeks) in patients with neovascular (wet) AMD. Thus, Eylea injection, which is the original biopharmaceutical of ALT-L9, was set as the comparator, and it was planned to enrol 15 subjects each in the study group and the control group, totalling 30 subjects.

Participant flow and numbers analysed

Disposition of Subjects

In this clinical study, 43 subjects were screened, 15 subjects of whom failed. Accordingly, 28 subjects were randomised to the study group and the control group with 14 subjects per group. All randomised subjects received the IP and completed the clinical study without withdrawal.

All randomised subjects completed the clinical study without any withdrawal. Thus, the Safety set included a total of 28 subjects (study group: 14 subject, control group: 14 subjects). The FAS, the main population of the efficacy evaluation, included a total of 28 subjects (study group: 14 subjects, control group: 14 subjects), and the PPS included a total of 27 subjects (study group: 13 subjects, control group: 14 subjects) as 1 subject (study group) was excluded for 'Tests not performed'.

Protocol Deviations

In this clinical study, 2 major protocol deviations were identified from 1 subject (study group) after randomisation.

Baseline data

Demographic information and other baseline characteristics

In this clinical study, 75.00% (21/28 subjects) of the subjects were male and 25.00% (7/28 subjects) were female, with males accounting for a larger proportion. The mean age was 72.57±6.64 years with a minimum of 62.00 years and a maximum of 87.00 years.

For drinking status, 39.29% (11/28 subjects) of the subjects were 'Current', 21.43% (6/28 subjects) were 'Former', and 39.29% (11/28 subjects) were 'Never'. The mean duration of drinking for 17 subjects who were 'Current' or 'Former' for drinking status was 37.47±12.43 years with a minimum of 13.00 years and a maximum of 50.00 years.

For smoking status, 10.71% (3/28 subjects) of the subjects were 'Current', 64.29% (18/28 subjects) were 'Former', and 25.00% (7/28 subjects) were 'Never'. The mean duration of smoking for 21 subjects who were 'Current' or 'Former' for smoking status was 25.81±13.77 years (a minimum of 6.00 years and a maximum of 60.00 years), and the mean cigarette consumption was 0.83±0.28 packs per day (a minimum of 0.2 packs per day and a maximum of 1.00 pack per day). The mean period of neovascular (wet) AMD was 53.05±31.94 month (a minimum of 13.78 months and a maximum of 113.26 months), which amounts to 4.42±2.66 years (a minimum of 1.15 years and a maximum of 9.44 years). In the result of sex, age, drinking status, smoking status, and period of neovascular (wet) AMD for the Safety set, there was no statistically significant difference between the two groups.

Past medical history

In this clinical study, 17.86% (5/28 subjects, 10 cases) had past medical history. By treatment group, 21.43% (3/14 subjects, 6 cases) of the study group and 14.29% (2/14 subjects, 4 cases) of the control group had past medical history; there was no statistical significance between the two groups (p-value=1.0000).

The most common past medical history was eye disorders in 10.71% (3/28 subjects, 5 cases) per SOC and cataract 7.14% (2/28 subjects, 4 cases) per PT.

Ongoing medical history

In this clinical study, 96.43% (27/28 subjects, 147 cases) had ongoing medical history. By treatment group, 100.00% (14/14 subjects, 66 cases) of the study group and 92.86% (13/14 subjects, 81 cases) of the control group had ongoing medical histories; there was no statistical significance between the two groups (p-value=1.0000).

Per SOC, the most common ongoing medical history was eye disorders in 71.43% (20/28 subjects, 37 cases), followed by metabolism and nutrition disorders in 64.29% (18/28 subjects, 23 cases) and vascular disorders in 53.57% (15/28 subjects, 16 cases). Per PT, the most common ongoing medical history was hypertension in 53.57% (15/28 subjects, 15 cases), followed by hyperlipidaemia in 42.86% (12/28 subjects, 12 cases) and benign prostatic hyperplasia 42.86% (12/28 subjects, 12 cases).

Prior medications

All subjects who participated in this clinical study had administration history of prior medications [100.00% (28/28 subjects, 248 cases)].

Per Level 2 (Therapeutic) in Level 1 (Anatomical), the most common prior medication was 'ophthalmologicals in sensory organs' in 100% (28/28 subjects, 109 cases), followed by 'lipid modifying agents in cardiovascular system' in 46.43% (13/28 subjects, 14 cases) and 'diagnostic agents in various' in 42.86% (12/28 subjects, 12 cases).

Prior therapies

Only 1 subject in the control group received prior therapies (1 case), which was paracentesis eye in the investigations.

Concomitant medications

All subjects who participated in this clinical study had administration history of concomitant medications [100.00% (28/28 subjects, 469 cases)].

Per Level 2 (Therapeutic) in Level 1(Anatomical), the most common concomitant medication was 'ophthalmologicals in sensory organs' in 100% (28/28 subjects, 322 cases), followed by 'lipid modifying agents in cardiovascular system' in 46.43% (13/28 subjects, 15 cases) and 'diagnostic agents in various' in 46.43% (13/28 subjects, 13 cases).

Concomitant therapies

Only 1 subject in the control group received concomitant therapies (1 case), which was contact lens therapy in the surgical and medical procedures.

Number of prior administrations of anti-VEGF medicine

All subjects who participated in this clinical study had prior administration history of anti-VEGF medicine in the study eye. The mean number of prior administrations was 24.64±13.92 doses in the study group and 16.79±8.72 doses in the control group; there was no statistical significance between the two groups (p-value=0.0851).

The most frequently administered anti-VEGF medicine was bevacizumab, followed by aflibercept and ranibizumab. The mean number of administrations for each anti-VEGF medicine was 11.85±8.81 doses in 92.86% (13/14 subjects, 154 cases) of the study group and 14.50±6.65 doses in 57.14% (8/14 subjects, 116 cases) of the control group for bevacizumab; 14.10±8.72 doses in 71.43% (10/14 subjects, 141 cases) of the study group and 10.00±6.73 doses in 50.00% (7/14 subjects, 70 cases) of the control group for aflibercept; and 7.14±5.87 doses in 50.00% (7/14 subjects, 50 cases) of the

study group and 6.13±4.09 doses in 57.14% (8/14 subjects, 49 cases) of the control group for ranibizumab. There was no statistical significance in the number of prior administrations for each anti-VEGF medicine between the two groups.

Only 14.29% (2/14 subjects, 2 cases) of the control group concomitantly received 1.00±0.00 dose of ranibizumab which was administered in the fellow eye.

Pregnancy test

Since all 7 female subjects who participated in this clinical study were postmenopausal, no pregnancy test was performed.

Physical examination

In the result of physical examination conducted at screening, the mean height was 164.72±7.51 cm (a minimum of 143.60 cm and a maximum of 177.40 cm), and the mean weight was 66.39±9.25 kg (a minimum of 48.60 kg and a maximum of 85.30 kg); there was no statistical significance between the two groups (p-value=0.6310 and 0.3730, respectively). All body systems were Normal/NCS.

Laboratory tests

Laboratory test items showing statistical significance between the two groups were RDW (p-value=0.0497) and MPV (p-value=0.0057) in haematology and chloride (p-value=0.0460), magnesium (p-value=0.0453), total protein (p-value=0.0041), and insulin (p-value=0.0215) in blood chemistry. However, laboratory test values of all subjects, except for creatinine kinase level of one subject, were 'Normal/NCS'. Creatinine kinase level of one subject was CS only at screening and 'Normal/NCS' at all the subsequent visits.

Virus serology test

The virus serology results of subjects who participated in this clinical study were negative for all of HAV-IgM, HBsAg, HCV Ab, and HIV-Ag/Ab, showing that no subject was infected with the viruses. Also, all of the subjects were positive for HAV-IgG, indicating they were immune to hepatitis A.

Vital signs

In the result of vital signs measured at the screening visit, the mean body temperature was 36.45±0.26℃; the mean systolic and diastolic blood pressure was 130.18±14.18 mmHg and 73.82±9.42 mmHg, respectively; the mean pulse rate was 76.75±12.09 beats/min; and the mean respiratory rate was 18.82±0.98 breaths/min. There was no statistical significance in each item between the two groups.

Ophthalmological examination

The result of FA, ICGA, SD-OCT, BCVA, slit lamp microscopy, tonometry, fundoscopy and fundus photography at the screening visit showed no statistical significance between the two groups.

Measurement of treatment compliance

As the IP was directly administered into the study eye of the subject by the investigator via intravitreal injection in this clinical study, questionnaire to check treatment compliance was not planned. In addition, if a subject did not receive the IP at the scheduled institution visit, the subject was to be withdrawn; however, there were no subjects who were withdrawn because they did not receive the IP at the scheduled regular visit in this clinical study.

Extent of Exposure

In this clinical study, it was planned to administer a total of 3 doses of the IP at 4 weeks intervals, and all subjects in the Safety set received all scheduled doses.

Outcomes and estimation

Primary Efficacy Evaluation Endpoint

Change from baseline in BCVA at the end of administration at Week 12

The primary efficacy evaluation endpoint in this clinical study, 'Change from baseline in BCVA at the end of administration at Week 12', was analysed on the FAS (main population) and the PPS (secondary population). In the FAS, the mean 'changes (Week 12 - baseline) from baseline in BCVA at the end of administration at Week 12' were 3.50±5.24 letters in the study group and 2.86±9.69 letters in the control group, showing statistically significant increase within the group (p-value=0.0267 and 0.0256, respectively) in both treatment groups. In addition, the mean change in BCVA was greater in the study group than in the control group, but there was no statistical significance between the two groups (p-value=0.6446).

In the PPS, the mean 'changes from baseline in BCVA at the end of administration at Week 12' were 4.23±4.66 letters in the study group and 2.86±9.69 letters in the control group, showing statistically significant increase within the group (p value= 0.0066 and 0.0256, respectively) in both treatment groups at Week 12 from baseline. In addition, the mean change in BCVA was greater in the study group than in the control group, but there was no statistical significance between the two groups (p-value=0.8454).

Secondary Efficacy Evaluation Endpoints

Change from Baseline in BCVA at Each Assessment Time Point (Day 1, Day 7, Week 4, Week 8, and Week 16)

The 'Change from baseline in BCVA at each time point' was analysed on the FAS (main population) and the PPS (secondary population). In the FAS, the mean 'change from baseline in BCVA at each time point' increased in both the study group and the control group, and the largest mean change in BCVA was observed at Week 16 in both the study group (3.21±7.52 letters) and the control group (2.64±9.56 letters). Also, the mean change in BCVA statistically significantly increased from baseline within the group at Week 8 and Week 16 in the control group (p-value=0.0342 and 0.0320, respectively), and there was no statistical significance between the two groups at all time points.

In the PPS, the mean 'change from baseline in BCVA at each time point' increased in both the study group and the control group, and the largest mean change in BCVA was observed at Week 16 in both the study group (4.08±7.06 letters) and the control group (2.64±9.56 letters). Also, the mean change in BCVA statistically significantly increased from baseline within the group at Week 16 in the study group and at Week 8 and Week 16 in the control group (p-value=0.0366, 0.0342 and 0.0320, respectively), and there was no statistical significance between the two groups at all time points.

Change from Baseline in Fovea Centralis Thickness at Each Assessment Time Point

The change from baseline in fovea centralis thickness at each time point was analysed on the FAS (main population) and the PPS (secondary population). In the FAS, the mean fovea centralis thickness decreased from baseline at each time point in both the study group and the control group, and the largest mean change in fovea centralis thickness was observed at Week 12 (-148.29±141.37) in the

study group and at Week 8 (-113.07±136.39) in the control group. Furthermore, in both the study group and the control group, the mean fovea centralis thickness statistically significantly decreased from baseline within the group at Day 7, Week 4, Week 8, Week 12, and Week 16. At Week 16, the study group showed a statistically significant decrease in the change in fovea centralis thickness, compared to the control group (p-value=0.0308), but there was no statistical significance at the other time points.

In the PPS, the mean fovea centralis thickness also decreased from baseline at each time point in both the study group and the control group, and the largest mean change in fovea centralis thickness was observed at Week 12 (-156.69±143.45 µm) in the study group and at Week 8 (-113.07±136.39 µm) in the control group. Furthermore, in both the study group and the control group, the mean fovea centralis thickness statistically significantly decreased from baseline within the group at Day 7, Week 4, Week 8, Week 12, and Week 16. At Week 16, the study group showed a statistically significant decrease in the change in fovea centralis thickness, compared to the control group (p-value=0.0256), but there was no statistical significance, at the other time points.

Percentage of Subretinal Fluid and/or Intraretinal Fluid at Each Assessment Time Point Compared to the Baseline

The percentage of subretinal fluid or intraretinal fluid at each time point compared to the baseline was analysed on the FAS (main population) and the PPS (secondary population). In the FAS, in the study group, percentage of subjects with 'Yes' to subretinal fluid at each time point either was maintained or decreased until Week 12 after the baseline, showing the lowest percentage of 14.29% (2/14 subjects) at Week 12, and it then increased to 42.86% at Week 16. In the control group, percentage decreased until Week 8 after the baseline, showing the lowest percentage of 28.57% (4/14 subjects) at Week 8 and Week 12, and it then increased to 64.29% at Week 16. There was no statistical significance between the two groups at each time point.

Furthermore, in the study group, percentage of subjects with 'Yes' to intraretinal fluid at each time point either was maintained or decreased until Week 16 after the baseline, showing the lowest percentage of 14.29% (2/14 subjects) at Week 16. In the control group, percentage either was maintained or decreased until Week 8 after the baseline, showing the lowest percentage of 14.29% (2/14 subjects) at Week 8 and Week 12, and it then increased to 42.86% at Week 16. There was no statistical significance between the two groups at each time point.

In the PPS, percentage of subjects with 'Yes' to subretinal fluid at each time point either was maintained or decreased until Week 12 after the baseline, showing the lowest percentage of 15.38% (2/13 subjects) at Week 12, and it then increased to 46.15% at Week 16 in the study group. In the control group, percentage decreased until Week 8 after the baseline, showing the lowest percentage of 28.57% (4/14 subjects) at Week 8 and Week 12, and it then increased to 64.29% at Week 16. There was no statistical significance between the two groups at all time points.

Furthermore, in the study group, percentage of subjects with 'Yes' to intraretinal fluid at each time point either was maintained or decreased until Week 16 after the baseline, showing the lowest percentage of 15.38%(2/13 subjects) at Week 16. In the control group, it either was maintained or decreased until Week 8 after the baseline, showing the lowest percentage of 14.29% (2/14 subjects) at Week 8 and Week 12 and then increased to 42.86% at Week 16. There was no statistical significance between the two groups at all time points.

Percent Change in Choroidal Neovascularisation Lesion at Week 12 Compared to Screening

The change in the 'ratio of CNV size to total lesion size' was checked and change status in CNV lesion was evaluated as 'Unchanged, Worsened and Improved'. In the FAS, in the study group, 'Improved'

was 42.86% (6/14 subjects), 'Unchanged' was 50.00% (7/14 subjects), and 'Worsened' was 7.14% (1/14 subject). In the control group, 'Improved' was 28.57% (4/14 subjects), 'Unchanged' was 57.14% (8/14 subjects), and 'Worsened' was 14.29% (2/14 subjects). The percentage of subjects with improvement was higher in the study group than in the control group, but there was no statistical significance between the two groups (p value= 0.7575).

In the PPS, in the study group, 'Improved' was 46.15% (6/13 subjects), 'Unchanged' was 46.15% (6/13 subjects), and 'Worsened' was 7.69% (1/13 subject). In the control group, 'Improved' was 28.57% (4/14 subjects), 'Unchanged' was 57.14% (8/14 subjects), and 'Worsened' was 14.29% (2/14 subjects). The percentage of subjects with improvement was higher in the study group than in the control group, but there was no statistical significance between the two groups (p value= 0.6497).

2.4.6. Discussion on clinical efficacy

The applicant has performed two clinical trials to support the development of the proposed biosimilar, a first-in-human phase I trial for safety (ALT-L9-01) and a phase III trial (ALT-L9-03). The assessment of efficacy will be mainly based on results from the phase III study with supportive data from the phase I study, since the evaluation of efficacy was the primary objective in the phase III study (considered pivotal) whereas the evaluation of efficacy was a secondary objective in the phase I study, performed only in 28 patients.

No GCP inspection related to these specific clinical studies were carried out by the European Medicines Agency at the time of the submission of this application. There were on-site GCP inspections conducted by BASG (Austrian Federal Office for Safety in Health Care) at one clinical site in Austria in 2024 for the ALT-L9-03 Phase 3 study, and by SUKL (State Institute for Drug Control) at one clinical site in the Czech Republic in 2024. No critical findings were identified during either inspection. Based on the review of clinical data, the need for a GCP inspection of the clinical trials included in this dossier was not identified.

ALT-L9-03 Phase 3 trial

The applicant has performed a phase 3, multicentre, double-masked, randomised, parallel-group clinical study to evaluate the proposed biosimilar, ALT-L9, to the reference product Eylea in patients. Study ALT-L9-03 was ongoing at the time of the initial dossier submission. The applicant initially provided an interim CSR covering up to 32 weeks of the data, followed by the final CSR covering up to week 52.

The study was conducted in subjects with neovascular age-related macular degeneration (nAMD). nAMD is one of the approved indications of Eylea in the EU. Other approved indications include retinal vein occlusion (RVO), diabetic macular oedema (DME) and choroidal neovascularisation (CNV). Studies with the reference product demonstrated that the treatment effect of aflibercept was largest in patients with nAMD (comparison against placebo). nAMD is therefore likely the most sensitive of the approved indications to detect any differences between the treatments in terms of clinical efficacy. The receptor and mechanism of action of aflibercept are the same across different ophthalmological indications approved for the reference product Eylea and aflibercept is directly delivered at its site of action. Since nAMD patients are generally considered a sensitive population for assessing similarity in clinical efficacy of aflibercept, it is agreed that if similarity is demonstrated in nAMD patients, the findings can be extrapolated to other indications approved for Eylea. Eylea 40 mg/mL solution for injection in pre-filled syringe is also approved for the treatment of retinopathy of prematurity (ROP) however this indication is not being sought by the applicant for Eyluxvi 40 mg/mL solution for injection in a vial.

Only treatment-naïve patients were to be included in the study, as agreed during the scientific advice procedure. A treatment-naïve nAMD population in which a significant effect on visual acuity is anticipated is regarded a sensitive and reasonable patient population to assess clinical biosimilarity of the biosimilar to the reference product.

The inclusion criterion for BCVA is 20/40 – 20/200 (≤73 and ≥34 ETDRS). The lower BCVA limit of 20/200 represents the limit of legal blindness, below which high variability in ETDRS is reported, while the upper limit leaves room for a 15-letter improvement in visual acuity. These limits are considered adequate for the primary efficacy endpoint. Following scientific advice inclusion and exclusion criteria have been updated, including patients being excluded if they had fibrosis that exceeded 50% of the total lesion size in the study, patients that were expected to need anti-VEGF treatment in the fellow eye before week 8 (primary analysis timepoint) were excluded to prevent additive effects, and any ambiguity around whether or not patients would be truly treatment naïve has been removed.

The reference product is Eylea, from Germany. The selected 2 mg dose is acceptable; it is the recommended dose in nAMD. The route of administration is IVT and is in line with the route of administration of the reference product. The posology is q8w IVT, after the loading phase of 3 injections q4w, also in line with the reference product. However, a pre-filled syringe (PFS) was used for the reference product administration, compared to a vial for the test product. The PFS presentation for the reference product was added to the vial presentation, however it is agreed that as both products contain the same active substance and use the same route of administration with sufficient training on proper handling and injection techniques, this should not have impacted the clinical results.

Subjects were randomised in a 1:1 ratio to either ALT-L9 or aflibercept. Randomisation was stratified by geographic region where the subject was enrolled (Europe vs Asia Pacific), BCVA ETDRS letter count recorded at baseline (<64 letters vs ≥64 letters), and CST at screening (<300 microns vs ≥300 microns). Following scientific advice, the applicant has decided not to include a treatment switch within the trial which is accepted. The trial was blinded to subjects and research staff, but not blinded to staff who prepare and administer the treatments due to the different presentations of the test and reference products.

The efficacy assessment methods of BVCA, SD-OCT, fundus photography and fluorescein angiography are standard ophthalmology assessments and are considered acceptable.

The applicant did not perform a usability study which is accepted as the administration and product information is generally the same as for the reference product.

Overall, the study design of Phase 3 study is considered adequate to establish similarity between ALT-L9 and the reference product Eylea.

The primary endpoint was the change from baseline in BCVA at Week 8 as measured by the ETDRS letter score which is considered appropriate. Change from baseline in BCVA is a continuous endpoint which can detect improvement or deterioration in the disease status and is considered to be a sensitive endpoint to detect differences between the biosimilar candidate and the reference product.

From the pivotal VIEW1 and VIEW2 studies conducted with the reference product, it is evident that the efficacy plateau is essentially reached after 12-16 weeks. The selected time point for the efficacy comparison at week 8, on the other hand, lies in the ascending part of the response curve and is therefore considered sufficiently sensitive to detect any differences between treatments.

Secondary endpoints included the change from baseline in BCVA, CST, subretinal and intraretinal fluid and CNV at different timepoints. Following scientific advice, the applicant is also reporting the proportion of subjects who gained/lost ≥ 5 or 10 letters in BCVA from baseline at the different study visits, and not just those who gained/lost ≥15 BCVA letters as was originally proposed.

Since the investigation of changes in central retinal thickness is considered highly important in the assessment of potential differences between treatments from a pharmacodynamic perspective, the Scientific Advice (EMA/SA/0000063713) gave several recommendations with regard to this secondary efficacy endpoint. As recommended in the EMA Scientific Advice, the central subfield thickness (CST) was defined as the average retinal thickness within 1-mm diameter area around the foveolar centre point from retinal pigment epithelium to internal limiting membrane, inclusively, and it was assessed (among other timepoints) at Week 4, which is considered a sensitive time point on the rising scale of the response curve. In addition, to ensure consistency in the used equipment and protocol procedure, the SD-OCT machine used for an individual subject was not to change for the duration of the study and all SD-OCT images were obtained by trained and study-certified site personnel at the study site and forwarded to the central reading centre for independent standardised analysis and storage. The applicant did not formally compare the CST difference to a pre-defined equivalence margin, as recommended in the EMA Scientific Advice, but this is not considered to pose any question about biosimilarity.

The secondary endpoints are adequately defined to further support biosimilarity assessment and the maintenance of efficacy over time and are supported. The same estimands are used for both primary and secondary endpoints.

The main efficacy analyses were performed on both the ITT and PPS analysis sets.

Equivalence would be concluded if the 95% CI of the primary endpoint at Week 8 was within the predefined equivalence margin of ±3.49 letters. This follows scientific advice received, where it was pointed out that ideally an equivalence margin around 3, but an equivalence margin of ±3.49 is in a reasonable range for study planning. BCVA of 5 letters is generally considered as clinically significant and the 3.49 letter margin is well away from the 5 letters, it was therefore agreed that 3.49 letters in BCVA has little clinical relevance and the proposed margin was thus considered acceptable. Although not required by EMA, the 90% CI was also provided (for US applications).

The sample size calculation of 410 patients is acceptable.

After data unblinding, a programming error was identified affecting immunogenicity data, but this did not affect the analysis of the primary endpoint.

431 patients were recruited to the trial (216 in the ALT-L9 group and 215 in the Eylea group). A low number of subjects discontinued the study or treatment, with similar numbers discontinued in both treatment arms. The most common reason for discontinuation of the study treatment and the study overall was adverse events (2.8% each).

A comparable number of subjects had major protocol deviations, the most common protocol deviations were related to 'study procedure/other', the majority of these were reported after the interim report and should not have impacted of the primary analysis. 6% in the test arm versus 4% in the reference arm were excluded from the PPS analysis due to protocol deviations.

Baseline characteristics of age, sex, race, country, height, weight and BMI were well balanced across both treatment groups. Ongoing and history of non-ocular and ocular events were well reasonably well balanced across both treatment arms. The most common ongoing non-ocular event being hypertension affecting 64% and 63% of patients in the test and reference arms. The most common ongoing ocular events apart from nAMD being dry AMD (64% and 62%), cataracts (45% and 45%) and Pseudophakia (38% and 33%) patients in the test and reference arms respectively. The most common ocular interventions were cataract surgery (38% and 33%) and laser treatment (7% and 7%).

The percentage of patients receiving concomitant medications was also well balanced across treatment arms, the most common con meds were povidone-iodine (77% and 74%) and tropicamide (67% and

68%). Treatment compliance was very high, with >93% of patients in both treatment arms being compliant with receiving IMP throughout the study.

Results for the primary endpoint demonstrated that ICE 1 (death), 2 (discontinuation due to lack of efficacy), 4 (missed IMP administration) and 6 (wrong IMP administered) did not occur by week 8. The remaining ICEs, ICE 3 (discontinuation for reasons other than lack of efficacy), 5 (Study treatment administration outside of ± 7-day window) and 7 (prohibited medications), occurred in low and comparable numbers across the treatment arms (14% versus 12% in test and reference arms). Baseline BCVA was comparable across both treatment arms, 59 and 60 in the test and reference arms, at week 8 BVCA increased by 6 and 8 to 65 and 68.

For the primary analysis, the LSM difference for the adjusted change from baseline in BCVA at Week 8 demonstrated the primary estimand was -2.092, the 95% CI was (−3.431, −0.753) which lay within the predefined margin of ±3.49 letters, therefore demonstrating bioequivalence between the test and the reference product. Similar results were obtained with the secondary and tertiary estimands.

Similar results were also obtained for the sensitivity analyses where the 95% CIs lay within the predefined margin of ±3.49 letters when evaluating the change from baseline in BCVA of the study eye at Week 8 with LOCF, MMRM, PPS and the correct reading of stratification factor for both the ITT and PP sets for all estimands; with the exception of LOCF for the primary estimand, which had a 95% CI of -3.540, -0.862, just shy of the pre-specified margins. It should be noted that the LOCF approach has several disadvantages, since the bias depends on many factors (including true evolutions after dropout and proportion of missingness in the treatment arms) and it does not necessarily yield a conservative estimation of the treatment effect. In addition, the imputation may also distort the variance structure. Therefore, since the primary efficacy analysis used a multiple imputation method and only the sensitivity analysis using the LOCF approach failed to fall within the predefined margin, globally it is considered that the results support the results of the primary endpoint. Tipping point analysis showed that the handling of missing data as MAR under treatment policy approach is appropriate and the efficacy response was robust to stress testing of assumptions. When a shift of 10 letters or more occurred in the ALT-L9 group, the 90% and 95% CIs were contained entirely within the predefined margin up to a maximum shift of 16 letters in the Eylea arm.

Sub-group analysis of the primary endpoint was presented by numerous different subgroup parameters. Results did not support bioequivalence for many of subgroups assessed, however assessments are limited by smaller sample sizes. Overall, however, despite many of the sub-group analyses failing to demonstrate bioequivalence, the primary endpoint and associated sensitivity analyses can be considered as demonstrating bioequivalence between the test and the reference product.

Secondary results were available for up to week 52. Up to this timepoint, results demonstrated that ICE 2 (discontinuation due to lack of efficacy) did not occur. The remaining ICEs occurred in low and comparable numbers across the treatment arms (36% versus 34% in test and reference arms). The 95% CI of the change from baseline in BCVA up to week 40 lay within the predefined bioequivalence margin of ±3.49 letters for all estimands, after week 40, results did not support bioequivalence. Results appeared to have plateaued by after week 8. Similar results were also obtained for sensitivity analyses (multiple imputation for BCVA=0) and the PPS dataset. In line with the primary results, results did not support bioequivalence for many of the subgroups assessed.

When looking at the adjusted proportion of subjects who had lost at least 5, 10 and 15 letters at week 52, numbers affected were low overall (less than 11%, primary estimand), but higher in test arm comparable to the reference arm. When looking at the adjusted proportion of subjects who had gained letters at week 52, results were also comparable across both treatment arms; 69% and 73% (≥5

letters), 42 and 45% (≥10 letters), 19 and 22% (≥15 letters) in the test and treatment arms respectively.

The next secondary endpoint of change from baseline in CST demonstrated similar results across both treatment arms with a maximum mean reduction at week 8: from 348 to 223 microns in the test arm and from 351 to 232 microns in the reference arm. Decreases in CST thickness were observed up to week 52 (ITT population). The percentage of patients with a reduction from baseline in sub or intraretinal fluids was also similar across both treatment arms with a maximum mean reduction at week 8: 100% to 46% in the test arm and 100% to 48% in the reference arm. Reduced levels of sub or intraretinal fluids were evident up to week 52. The adjusted change from baseline in total size of CNV area was also similar across both treatment arms, by week 52 there was a reduction of 0.926mm^2 and 1.20mm^2 while CNV leakage reduced from 100% to 57% and 49% in the test and reference arms respectively.

Overall, the efficacy results can generally be considered as demonstrating bioequivalence between the test and the reference product.

ALT-L9-01 – Phase I trial

For biosimilar applications for a bioequivalence PK trial, healthy volunteers are preferable and considered the most homogenous and sensitive population for detection of any potential differences between the test and reference compound. However, given the low systemic absorption of aflibercept and the locally acting nature of the drug in the eye, a standard bioequivalence PK trial is not appropriate. Instead, the applicant has performed a randomised, double-masked, active-controlled, parallel group phase I trial in nAMD. As a first in human study the main objective of this trial was safety, however supportive efficacy endpoints were also included. It is noted that other aflibercept biosimilar products performed only a phase 3 trial which is also considered acceptable.

In contrast to the phase 3 trial, this trial recruited patients previously treated with anti-VEGF inhibitors. Treatment-experienced patients may have reached the plateau in terms of maximal gain in visual acuity and may well maintain their visual acuity with less frequent dosing, which makes them a less sensitive population. In addition, while it would be unethical to leave patients without treatment for more than the 8 weeks of the wash-out period, there may be some carry-over effects at the start of the study, particularly for those previously treated with anti-VEGF antibodies. This limits any interpretation of the efficacy results in this trial. Other inclusion and exclusion criteria for selecting nAMD patients are adequate.

All patients were from Korea. As this is a supportive biosimilar study, any racial differences to the EU population are of less relevance. The double-blind nature of the trial is appropriate.

The reference product is Eylea, from Germany. The selected 2mg dose is acceptable. It is the recommended dose in nAMD. The route of administration is IVT and is in line with the route of administration of the reference product. Patients will receive 3 doses at 4-week intervals. In contrast to the phase 3 trial, for this trial the vial presentation of the reference was used which is preferable. Other aspects of the trial design are generally acceptable.

The main objective of the study was to assess safety of the proposed biosimilar. The main efficacy endpoint is the change from baseline in BCVA (ETDRS) at week 12. BCVA at week 8 would be a preferred endpoint as it represents a steeper part of the pharmacodynamic response curve for aflibercept, however week 8 is included as a secondary efficacy endpoint and is therefore accepted.

Other efficacy endpoints include the change from baseline in fovea centralis thickness (FCT), the percentage of patients with subretinal fluid and intraretinal fluid, at set timepoints, and the change in

CNV lesions, all of which are clinically relevant endpoints. These are similar endpoints to the phase 3, except for FCT instead of CST.

The planned sample size was 30 subjects and is appropriate. The statistical analysis of the trial is accepted given that this is a small FIH phase I supporting study where the primary objective is assessing safety. There were no patients discontinued or withdrawn from the trial. Only 1 patient was excluded from the PPS analysis due to protocol deviations where immunogenicity and laboratory testing was not performed. Treatment compliance was 100%.

Baseline demographics and characteristics were reasonably well balanced across the two treatment arms given the limited sample size. Although there were some differences including less females recruited to the test arm compared to the reference arm (14% versus 36%) and patients in the test arm having a longer duration of disease compared to patients in the reference arm (5.1 years versus 3.8 years).

The majority of patients were receiving concomitant medications for a variety of non-eye indications however these were generally balanced across treatment arms and were unlikely to have a significant impact on the eye. All patients had previous anti-VEGF administrations in the study eye including ranibizumab, bevacizumab and aflibercept, however patients in the test arm had a larger median number of administrations in the study eye compared to the reference arm (25 versus 17), this may be linked to the longer disease duration in these patients.

The primary endpoint was change from baseline in BCVA at week 12. Results demonstrated an increase of 3.5 and 2.9 letters in the test and reference treatment arms in the FAS analysis. Similar results were obtained in the PPS analysis. At baseline, the letter scores were higher in the test group. Since this was not the pivotal clinical study, a comparability margin to demonstrate equivalence between the study group and the control group was not set. Although there was a higher increase observed in the test arm, results are generally comparable and there was no statistically significant difference between the arms. A secondary endpoint examined the mean change in BCVA over time with results showing improvements at all timepoints assessed with the greatest increase in both arms at week 16. At week 8, the timing of the primary endpoint in the pivotal phase 3 trial, FAS results demonstrated an increase of 0.5 and 1.4 letters in the test and reference treatment arms. This is a considerably lower increase compared to the phase 3 trial, as mentioned previously this may be due to the patients being exposed to anti-VEGF inhibitors and potential carry-over effects in the phase 1 trial.

Other secondary endpoints included the change from baseline in fovea centralis thickness (FCT), results demonstrated a decrease at all timepoints assessed across both treatment arms, with the greatest decrease observed at week 12 in the test arm (-148 µm) and week 8 in the reference arm (-113 µm) in the FAS. Similar results were also obtained in the PPS. At week 16, when fovea centralis thickness was increasing again, there was a significant difference in results between the treatment arms in both analysis sets (-143 versus -69 µm in FAS).

The percentage of subretinal fluid decreased across both treatment arms with the largest decrease observed at week 12 in the test arm (14%) and week 8/12 (29%) in the reference arm in the FAS. The percentage of subretinal fluid began to increase again after these timepoints. The percentage of intraretinal fluid decreased across both treatment arms with the largest decrease observed at week 16 in the test arm (14%) and week 8/12 (14%) in the reference arm in the FAS. Similar results were also obtained in the PPS. There was no statistically significant difference across treatment arms at any timepoint.

Lastly, the change in the ratio of CNV size to total lesion size was assessed and a higher percentage of patients demonstrated an improvement from baseline at week 12 in the test arm (43%) compared to the reference arm (29%).

Overall, the proposed biosimilar resulted in a larger increase from baseline in BCVA at week 12, a larger decrease in fovea centralis thickness and the percentage of patients with subretinal fluid, and a higher percentage of patients with improved CNV lesions when compared to the reference product. However, subject numbers are low and apart from fovea centralis thickness, the differences between the test and reference were not statistically significant.

The phase 1 study is considered supportive only as no formal efficacy statistical analyses has been performed and efficacy was not the primary endpoint.

2.4.7. Conclusions on the clinical efficacy

Overall, the clinical trial results, including primary and secondary endpoints, sensitivity analyses and subgroup analyses collectively demonstrate that ALT-L9 shows comparable results to Eylea, supporting its biosimilarity with regard to efficacy.

2.4.8. Clinical safety

The safety profile of ALT-L9 compared to the reference medicinal product was evaluated on data derived from 2 clinical studies, ALT-L9-01 (Phase 1) and ALT-L9-03 (Phase 3). The design and conduct of these studies are discussed in detail in section 2.4.5.2 and 2.4.5.6 of this report.

Data from the two studies were not pooled and were presented separately.

ALT-L9-03

Safety assessments were performed at the visits specified in the Schedule of Assessments, as per Table 14 below.

Table 14. Schedule of assessments

	Pre-treatment	Treatment period											EOS/ Early termination
Visit	1	2	3[a]	4	5	6	7[a]	8	9	10	11	12	13
Timepoint	Screening	D1 (Base-line)	D2	Week 1 (~D8)	Week 4 (~D29)	Week 8 (~D57)	Week 8 + 1 D (D58)	Week 16 (~D113)	Week 24 (~D169)	Week 32 (~D225)	Week 40 (~D281)	Week 48 (~D337)	Week 52 (D365)
Window (± D)	Up to 21 D before Visit 2			±3	±3	±3		±5	±5	±5	±7	±7	±7
Informed consent	X												
Eligibility criteria	X	X											
Medical history and demographics	X												
Physical examination[b]	X												X
Body weight, height, and body mass index	X												
Vital signs: heart rate and BP	X	X			X	X		X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA assessment (ETDRS protocol)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT[d]	X			X	X	X		X	X	X	X	X	X
SLE[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundus examination[f]	X	X	X		X	X	X	X	X	X	X	X	X
CFP[g]	X									X			X
FA[h]	X									X			X
IOP measurement[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry and hematology[j]	X				X	X			X				X
Urinalysis	X				X	X			X				X
Serum pregnancy test	X												
Urine pregnancy test[k]		X			X	X		X	X	X	X	X	X

	Pre-treatment	Treatment period											EOS/ Early termination
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7[a]**	**8**	**9**	**10**	**11**	**12**	**13**
Timepoint	**Screening**	**D1 (Base-line)**	**D2**	**Week 1 (~D8)**	**Week 4 (~D29)**	**Week 8 (~D57)**	**Week 8 + 1 D (D58)**	**Week 16 (~D113)**	**Week 24 (~D169)**	**Week 32 (~D225)**	**Week 40 (~D281)**	**Week 48 (~D337)**	**Week 52 (D365)**
Window (± D)	**Up to 21 D before Visit 2**			**±3**	**±3**	**±3**		**±5**	**±5**	**±5**	**±7**	**±7**	**±7**
Randomization		X											
ALT-L9/Eylea administration (study eye only)[l]		X			X	X		X	X	X	X	X	
Blood sample(s) for evaluation of immunogenicity (serum ADAs and NAbs)[m]		X			X	X		X		X			X
Blood samples for PK evaluation (3 times)[n]		X	X				X						
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA, antidrug antibody; AE, adverse event; BCVA, best-corrected visual acuity; BP, blood pressure; CFP, color fundus photography; D, Day; ETDRS, Early Treatment Diabetic Retinopathy Study; EOS, End-of-Study; FA, fluorescein angiography; IOP, intraocular pressure; IVT, intravitreal; NAb, neutralizing antibody; SD-OCT, spectral domain-optical coherence tomography; PK, pharmacokinetic; SLE, slit-lamp examination; WOCBP, women of childbearing potential.

a. The Day 2 and Week 8 (+1 day) visits were for the PK sub-population only.
b. A physical examination consists of a routine evaluation of organ systems (including head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems). At the Screening Visit, the physical examination included the collection of the subject's eye color (ie, light iris or dark iris).
c. BCVA is assessed in both eyes at the Screening and EOS Visits. At all other scheduled visits, BCVA is assessed in the study eye only.
d. SD-OCT assessment was conducted in both eyes at screening. At Weeks 1, 4, 8, 16, 24, 32, 40, 48, and 52/EOS, SD-OCT assessment is conducted in the study eye only.
e. SLE of the anterior segment was conducted in both eyes at screening and baseline. At all other scheduled visits, SLE is conducted in the study eye only.
f. Dilated fundus examination of posterior segment was conducted in both eyes at screening and baseline. At all other scheduled visits except Week 1, the dilated fundus examination of the posterior segment is conducted in the study eye only.
g. CFP assessment was conducted in both eyes at screening. At Weeks 32 and 52/EOS, CFP will be conducted in the study eye only. In the case of early termination, CFP does not have to be repeated if it was done within the previous 12 weeks.
h. FA assessment was conducted in both eyes at screening. At Weeks 32 and 52/EOS, FA assessment will be conducted in the study eye only. In the case of early termination, FA does not have to be repeated if it was done within the previous 12 weeks.
i. IOP was measured in both eyes at screening and will be measured at Week 52/EOS. At all other scheduled visits, the IOP is measured in the study eye.
j. It is recommended to take the blood samples after 8 hours of fasting.
k. For WOCBP, a serum pregnancy test was conducted at screening and analyzed at the central laboratory. Only subjects with a negative serum pregnancy test result were enrolled in the study. For WOCBP, a urine pregnancy test is used to confirm that subjects are not pregnant before dosing on each scheduled visit and at the EOS visit, or more frequently if required by country-specific legislation. The urine pregnancy tests are performed locally. If a urine pregnancy test result is positive or equivocal, a confirmatory serum pregnancy test is to be performed at the local laboratory.
l. Subjects are monitored onsite after each injection for approximately 30-60 minutes to assess any treatment toxicities and to perform appropriate management if needed. Between 30 and 60 minutes after the IVT injection, subjects are monitored for elevation in IOP using tonometry. Noncontact tonometry is allowed, but if IOP is >36 mm Hg, the result is to be confirmed by applanation tonometry (eg, Goldmann Applanation Tonometer, Tono-Pen) or iCare within the next 30 minutes.
m. Immunogenicity samples are collected from all randomized and treated subjects. Blood sampling is performed before dose administration for immunogenicity testing. Additional samples for the monitoring of immunogenicity are collected from subjects with any signs of intraocular inflammation, as these could indicate an immune reaction.
n. A subpopulation of ~40 subjects is included in the PK analysis. PK samples were collected for these subjects 3 times: baseline (before first IVT dose), Day 2 (24 hours ± 2 hours after the first IVT dose), and Week 8 + 1 day (24 hours ± 2 hours after the third IVT dose). The Day 2 and Week 8 (+ 1 day) visits were for the PK sub-population only.

These include vital signs, physical examinations, ophthalmological examination (SLE, IOP, and dilated fundus examination), clinical laboratory assessments (routine haematology and clinical chemistry, urinalysis, and immunogenicity), and monitoring and recording of the type, frequency, relatedness, and severity of all AEs (ocular, by study eye and fellow-eye, and non-ocular) and injection site reactions (ISRs). Adverse events of special interest (AESIs) were defined a priori and included arterial thromboembolic events (ATEs), non-ocular haemorrhages and all AEs relating to IVT injection related reactions, including but not limited to endophthalmitis, increases in IOP, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.

AEs were followed up until the event resolves or stabilised at a level acceptable to the investigator, even after study drug discontinuation.

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Safety assessments were performed at the visits specified in the Schedule of Assessments, as per Table 15 below.

Table 15. Schedule of assessments

Clinical Study Procedure	Screening	Baseline			Treatment Period				EOT	EOS
	Screening[1]	Visit 1[1]			Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	- 28 Days ~ - 1 Day	Day 0 Pre-dose	Day 0 Post-dose (1hr)	Day 0 Post-dose (3hrs)	Day 1	Day 7 (±1 Days)	Week 4 (±3 Days)	Week 8 (±3 Days)	Week 12 (±3 Days)	Week 16 (±3 Days)
Informed consent	○									
Demographic information	○									
Medical history	○	○								
Prior medications and therapies	○	○								
Vital signs[3]	○	○			○	○	○	○	○	○
Physical examination[4]	○	○					○	○	○	○
Laboratory tests[5]	○	○			○	○	○	○	○	○
Serum pregnancy test (for women of childbearing potential)	○								○	
FA[6,14]	○								○	
ICGA[7,14]	○								○	
SD-OCT[8,14]	○	○[2]			○	○	○	○	○	○
ETDRS BCVA[14]	○	○[2]			○	○	○	○	○	○
Slit lamp microscopy[10, 14]	○	○[2]			○	○	○	○	○	○
Tonometry[13,14]	○	○	○[12]		○	○	○	○	○	○
Funduscopy[14]	○	○	○[12]		○	○	○	○	○	○
Fundus photography[14]	○	○			○	○	○	○	○	○
Wash-out period[9]	○	○								
Inclusion/exclusion criteria	○	○								
Randomization		○								
IP administration		○					○	○		
Blood sampling for evaluation of PK characteristics[11]		○		○	○	○	○			
Blood sampling for immunogenicity assessment		○							○	
Concomitant medications and therapies		○	○	○	○	○	○	○	○	○
AE assessment		○	○	○	○	○	○	○	○	○

1) If possible, the procedures scheduled for the Screening Visit and Visit 1 could be performed on the same day.

2) The results of SD-OCT, ETDRS-BCVA, and slit lamp microscopy within 14 days prior to Visit 1 could be used.

3) Vital signs: Blood pressure, pulse rate, body temperature (by tympanic), and respiratory rate were measured, and blood pressure and pulse rate were measured after subjects rested in a sitting position for more than 5 minutes.

4) Physical examination: Height and weight were measured at the screening visit, and only weight was measured at every subsequent visit.

5) Laboratory tests: Laboratory test items were as follows. They were measured in a fasted state in the morning or at least 2 hours after meals.

- Hematology: WBC, RBC, Hemoglobin, Hematocrit, Platelets count, WBC differential count (Eosinophil, Basophil, Neutrophil, Lymphocyte, Monocyte), MCV, MCH, MCHC, RDW, MPV, ANC
- Blood chemistry: Sodium, Potassium, Calcium, Chloride, Magnesium, Phosphorus, Blood urea nitrogen, Creatinine, Uric acid, Total bilirubin, Direct bilirubin, Albumin, Total protein, Creatine kinase, ALT(SGPT), AST(SGOT), γ-GT, Alkaline phosphatase, Glucose, Insulin, Total cholesterol, HDL cholesterol, LDL cholesterol, Triglyceride, LDH, Carbon Dioxide, Estimated GFR, HbA1c(%), C-reactive peptide
  - Estimated GFR (eGFR) was calculated using the MDRD formula below.

$$\text{MDRD} = 175 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ [if female]} \times 1.212 \text{ [if Black]}$$

- Blood coagulation test: PT(INR), aPTT
- Urinalysis: pH, Specific gravity, Bilirubin, Urobilinogen, Nitrite, Glucose, Ketones, WBC(Leukocytes), Albumin/Protein (either Albumin or Protein), Hemoglobin/Occult blood (either Hemoglobin or Occult blood)
- Virus serology: Tests for HAV-IgM, HAV-IgG, HBsAg, HCV Ab, and HIV-Ag/Ab were performed at screening.

6) FA: After mydriatic was dropped in both eyes of subjects, they waited for 30 minutes to 2 hours until mydriasis. Then, contrast (fluorescein) was injected into a vein and fundus was observed using ophtalmoscope at the same time. The assessment items included CNV size to total lesion size, etc.

7) ICGA: After mydriatic was dropped in both eyes of subjects, they waited for 30 minutes to 2 hours until mydriasis. Then, contrast (indocyanine green) was injected into a vein and fundus was observed using ophtalmoscope at the same time. The assessment items included CNV size to total lesion size, etc.

8) SD-OCT: The presence of intraretinal fluid, subretinal fluid, and subretinal pigment epithelium fluid, occurrence of subretinal bleeding or fovea centralis bleeding, occurrence of retinal pigment epithelial tear or laceration, central circle thickness of the retina, etc. observed by imaging were assessed. The central circle of the retina was defined as a circle of 1 mm in diameter from the fovea centralis.

9) Wash-out period: All subject had wash-out period for at least 8 weeks from the last dose of anti-VEGF treatment administered prior to the screening visit to Visit 1 (Baseline, Day 0).

10) Slit lamp microscopy: The number of anterior chamber cells and level of flare observed during microscopy were assessed according to the SOIS criteria to determine the inflammatory markers.

11) Blood sampling for evaluation of PK characteristics: It was performed in a fasted state in the morning or at least 2 hours after meals. Blood sampling was performed before the first dose of the IP (could be performed along with blood sampling for laboratory tests) and 3 hours (window time: ±5 minutes) after the first dose of the IP at Visit 1 (Baseline, Day 0) and 24 hours (window time: ±1 hour) after the first dose of the IP at Visit 2 (Day 1). At Visit 3 (Day 7), it was performed along with blood sampling for laboratory tests, and at Visit 4 (Day 28), it was performed before the second dose of the IP.

12) Tonometry, Funduscopy: At post-dose (1 hr) of Visit 1 (Day 0), the tests were performed within 60 minutes after IP administration.

13) The normal range of tonometry is 9~20 mmHg.

14) At the Screening Visits, both eyes were tested, and from Visit 1, only the study eye was tested.

Safety assessments included the incidence of targeted AEs in the study eye at Week 12 after 3 doses of IP, and at each assessment time point after the first dose of the IP. A targeted AE was defined as "AEs requiring monitoring for the indication that were subject to the safety evaluation following IP administration in this clinical study" and included:

- Occurrence of ocular inflammation assessed as SOIS score of 4+ or higher
- Ocular inflammation assessed as SOIS score of 2 or 3+ that failed to reduce to
- SOIS score of 1+ or lower within 30 days from the date of onset
- Vision loss that exceeded 15 letters compared to BCVA evaluation at baseline prior to IP administration
- Sustained (exceeded 15 minutes) decline in light perception ability due to an increase of intra ocular pressure (IOP)
- IOP > 20mmHG and failed to return to the baseline IOP measured prior to IP administration within 7 days from the date of onset
- Occurrence of a new retinal tear or detachment

Other safety assessments included the incidence of AEs (study eye, fellow eye, and other), ADRs, ophthalmological examination (FA, ICGA, SD-OCT, SLE, tonometry, fundoscopy), laboratory tests (haematology, blood chemistry, blood coagulation test, virus serology, and urinalysis), vital signs (body temperature, blood pressure, pulse rate, and respiratory rate), and immunogenicity assessment [anti-drug antibody (anti-ALT-L9 antibody)] before the first dose of the IP and at Week 12 after IP administration.

2.4.8.1. Patient exposure

Table 16. Patient exposure

	Patients enrolled[a]	Patients exposed*	Patients exposed to the proposed dose range[b]	Patients with long term** safety data
ALT-L9-01 (active -controlled)	28	Total: N=28 ALT-L9: N=14 Eylea: N=14	Total: N=28 ALT-L9: N=14 Eylea: N=14	n/a
ALT-L9-03 (active -controlled)	431	Total: N=431 ALT-L9: N=216 Eylea: N=215	Total: N=407 ALT-L9: N=205 Eylea: N=202	Total: N=407 ALT-L9: N=205 Eylea: N=202

* Patients received at least 1 dose of active treatment
** Patients exposed to 48 weeks treatment
[a] Subjects randomised at Week 0
[b] Study ALT-L9-01: 2 mg IVT study eye q4w for total of 8 weeks; Study ALT-L9-03: 2 mg IVT study eye q4w at baseline, Week 4, and Week 8 and thereafter q8w at Weeks 16, 24, 32, 40, and 48 for 48 weeks

ALT-L9-03

Data through Week 52 of this study have been provided in the final CSR, dated 22/08/2024. Prior evaluation was based on interim data provided through Week 32.

All randomised subjects who receive at least 1 administration (full or partial) of the study drug were included in the Safety Analysis Set for this study. In total, 431 subjects were randomised and assigned

to study treatment. All (100%) subjects received at least 1 single IVT injection, as per protocol, of either ALT-L9 (216 subjects) or reference product (215 subjects) at a dose level of 2 mg/eye each.

A total of 407 subjects (94.4%) completed the study treatment through Week 48 (205 and 202 subjects for the ALT-L9 and Eylea groups, respectively). A total of 405 subjects (94.0%) completed the study through Week 52 (204 and 201 subjects in ALT-L9 and Eylea groups, respectively).

The mean extent of exposure was 99.6% for the ALT-L9 group and 99.9% for the Eylea group. The mean duration of exposure was 46.8 weeks for the ALT-L9 group and 46.7 weeks for the Eylea group. The mean total number of doses administered was 7.8 for both groups.

The proportion of subjects that discontinued study treatment was similar between groups; 11 (5.1%) and 13 (6.0%) subjects in the ALT-L9 and Eylea groups, respectively. The most common reasons for study treatment discontinuation in the ALT-L9 group were 'withdrawal of consent' (3 subjects; 1.4%) and 'adverse event' (3 subjects; 1.4%). The most common reason for study treatment discontinuation in the Eylea group was 'adverse event' (9 subjects; 4.2%).

The proportion of subject that discontinued the study was similar between groups; 12 (5.6%) and 14 (6.5%) subjects in the ALT-L9 and Eylea groups, respectively.

Subject baseline data are provided in section2.4.5.2 of this report.

ALT-L9-01

Full safety data have been provided for this completed study in the final CSR, dated 24/05/2022.

The safety analysis set included subjects whose safety-related data were evaluated at least once among the subjects who received the IP at least once after randomisation. In total, 28 subjects were randomised and assigned to study treatment. All 28 (100%) subjects received a total of 3 single IVT injections, as per protocol, of either ALT-L9 (14 subjects) or the reference product (14 subjects), both at a dose level of 2 mg. Each single IVT injection was administered every 4 weeks (at Day 0 [Visit 1], Week 4 [Visit 4], and Week 8 [Visit 5]). All 28 randomised subjects were included in the safety set.

Subject baseline data are provided in section 2.4.5.6 of this report, including history of prior administrations of anti-VEGF medicine with aflibercept, bevacizumab, and ranibizumab.

2.4.8.2. Adverse events

ALT-L9-03

Summaries for overall systemic and ocular AEs are presented in Table 17 and Table 18, respectively below.

Table 17. Overall summary of adverse events for systemic category (safety analysis set)

	ALT-L9 (N=216) n (%) e	Eylea (N=215) n (%) e	Overall (N=431) n (%) e
Any AEs	122 (56.5) 320	118 (54.9) 299	240 (55.7) 619
Any TEAEs	116 (53.7) 292	112 (52.1) 274	228 (52.9) 566
Any SAEs	25 (11.6) 29	25 (11.6) 31	50 (11.6) 60
Any treatment-related TEAEs	0	2 (0.9) 3	2 (0.5) 3
Any treatment-related SAEs	0	2 (0.9) 2	2 (0.5) 2
Any AESIs	2 (0.9) 2	7 (3.3) 8	9 (2.1) 10
Any TEAEs leading to discontinuation from the study treatment	2 (0.9) 2	7 (3.3) 8	9 (2.1) 10
Any TEAEs leading to discontinuation from study	3 (1.4) 3	6 (2.8) 8	9 (2.1) 11
Any TEAEs leading to death	1 (0.5) 1	0	1 (0.2) 1

Abbreviations: AE, adverse event; AESI, adverse event of special interest; e, number of events; IVT, intravitreal; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. A TEAE is defined as any event not present before the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment. AESIs included arterial thromboembolic events, non-ocular hemorrhages, and all AEs related to IVT injection-related reactions.
Source: Table 14.3.1.1.1

Table 18. Overall summary of adverse events for ocular category (safety analysis set)

	ALT-L9 (N=216) n (%) e	Eylea (N=215) n (%) e	Overall (N=431) n (%) e
Any AEs	90 (41.7) 137	75 (34.9) 115	165 (38.3) 252
Any TEAEs	90 (41.7) 137	75 (34.9) 114	165 (38.3) 251
Any SAEs	1 (0.5) 1	3 (1.4) 3	4 (0.9) 4
Any treatment-related TEAEs	3 (1.4) 3	3 (1.4) 5	6 (1.4) 8
Any treatment-related SAEs	0	0	0
Any AESIs	11 (5.1) 14	15 (7.0) 18	26 (6.0) 32
Any TEAEs leading to discontinuation from study treatment	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Any TEAEs leading to discontinuation from study	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Any TEAEs leading to death	0	0	0

Abbreviations: AE, adverse event; AESI, adverse event of special interest; e, number of events; IVT, intravitreal; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. A TEAE is defined as any event not present before the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment. AESIs included arterial thromboembolic events, non-ocular hemorrhages, and all AEs related to IVT injection-related reactions.
Source: Table 14.3.1.1.1

TYPE & FREQUENCY

The most common TEAEs (reported by >2% subjects overall) are summarised in Table 19 below, by category (systemic or ocular), SOC, and PT.

Table 19. Most common (reported by >2% subjects overall) treatment-emergent adverse events by category, SOC, and PT (safety analysis set)

SOC PT	ALT-L9 (N=216) n (%) e	Eylea (N=215) n (%) e	Overall (N=431) n (%) e
Category: Systemic			
At least 1 TEAE	116 (53.7) 292	112 (52.1) 274	228 (52.9) 566
Infections and infestations	41 (19.0) 65	42 (19.5) 51	83 (19.3) 116
Nasopharyngitis	11 (5.1) 11	21 (9.8) 23	32 (7.4) 34
COVID-19	11 (5.1) 14	3 (1.4) 3	14 (3.2) 17
Musculoskeletal and connective tissue disorders	20 (9.3) 30	23 (10.7) 32	43 (10.0) 62
Back pain	4 (1.9) 6	5 (2.3) 5	9 (2.1) 11
Nervous system disorders	17 (7.9) 23	17 (7.9) 29	34 (7.9) 52
Headache	7 (3.2) 8	4 (1.9) 5	11 (2.6) 13
Vascular disorders	17 (7.9) 20	15 (7.0) 17	32 (7.4) 37
Hypertension	11 (5.1) 13	10 (4.7) 11	21 (4.9) 24
Category: Ocular			
At least 1 TEAE	90 (41.7) 137	75 (34.9) 114	165 (38.3) 251
Eye disorders	83 (38.4) 120	70 (32.6) 99	153 (35.5) 219
Neovascular age-related macular degeneration	23 (10.6) 24	13 (6.0) 13	36 (8.4) 37
Visual acuity reduced	12 (5.6) 12	10 (4.7) 11	22 (5.1) 23
Cataract	8 (3.7) 8	4 (1.9) 5	12 (2.8) 13
Subretinal fluid	6 (2.8) 6	4 (1.9) 4	10 (2.3) 10

Abbreviations: e, number of events; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. A TEAE is defined as any event not present before the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment. If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
Source: Table 14.3.1.2.1.1

SEVERITY

Overall, in the systemic category, a higher proportion of TEAEs reported were mild (116 [26.9%] subjects) or moderate (90 [20.9%] subjects) in severity. Severe TEAEs were reported in 9 (4.2%) subjects in the ALT-L9 group and in 13 (6.0%) subjects in the Eylea group.

The most common severe TEAE in the systemic category was ischaemic stroke, reported for 1 subject in each treatment group; all other severe TEAEs were reported for 1 subject each in either treatment group.

A summary of severe TEAEs by SOC and PT for the systemic category is presented in Table 20.

Table 20. Severe treatment-emergent adverse events by system organ class and preferred term for category systemic (safety analysis set)

SOC PT	ALT-L9 (N=216) n (%)	Eylea (N=215) n (%)	Overall (N=431) n (%)
At least 1 severe TEAE	9 (4.2)	13 (6.0)	22 (5.1)
Infections and infestations	2 (0.9)	0	2 (0.5)
Pneumonia	1 (0.5)	0	1 (0.2)
Pneumonia aspiration	1 (0.5)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.5)	1 (0.2)
Spinal osteoarthritis	0	1 (0.5)	1 (0.2)
Nervous system disorders	1 (0.5)	3 (1.4)	4 (0.9)
Ischaemic stroke	1 (0.5)	1 (0.5)	2 (0.5)
Lumbar radiculopathy	0	1 (0.5)	1 (0.2)
Paresis	0	1 (0.5)	1 (0.2)
Trigeminal palsy	0	1 (0.5)	1 (0.2)
Vascular disorders	1 (0.5)	1 (0.5)	2 (0.5)
Arteriosclerosis	1 (0.5)	0	1 (0.2)
Orthostatic hypotension	0	1 (0.5)	1 (0.2)
Gastrointestinal disorders	1 (0.5)	2 (0.9)	3 (0.7)
Gastric ulcer haemorrhage	0	1 (0.5)	1 (0.2)
Intestinal haemorrhage	0	1 (0.5)	1 (0.2)
Pancreatitis acute	1 (0.5)	0	1 (0.2)
Renal and urinary disorders	1 (0.5)	0	1 (0.2)
Renal colic	1 (0.5)	0	1 (0.2)
Injury, poisoning and procedural complications	2 (0.9)	1 (0.5)	3 (0.7)
Humerus fracture	0	1 (0.5)	1 (0.2)
Accidental overdose	1 (0.5)	0	1 (0.2)
Rib fracture	1 (0.5)	0	1 (0.2)
Cardiac disorders	0	2 (0.9)	2 (0.5)
Atrial fibrillation	0	1 (0.5)	1 (0.2)
Acute myocardial infarction	0	1 (0.5)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.4)	5 (2.3)	8 (1.9)
Acute myeloid leukaemia	1 (0.5)	0	1 (0.2)
Glioma	1 (0.5)	0	1 (0.2)
Hormone-dependent prostate cancer	0	1 (0.5)	1 (0.2)
Lung adenocarcinoma	0	1 (0.5)	1 (0.2)
Lung cancer metastatic	0	1 (0.5)	1 (0.2)
Lung neoplasm malignant	0	1 (0.5)	1 (0.2)
Oesophageal carcinoma	1 (0.5)	0	1 (0.2)
Prostate cancer	0	1 (0.5)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	0	1 (0.2)
Chronic obstructive pulmonary disease	1 (0.5)	0	1 (0.2)
Skin and subcutaneous tissue disorders	0	1 (0.5)	1 (0.2)
Pemphigoid	0	1 (0.5)	1 (0.2)
Blood and lymphatic system disorders	0	2 (0.9)	2 (0.5)
Anaemia	0	1 (0.5)	1 (0.2)
Blood loss anaemia	0	1 (0.5)	1 (0.2)
Hepatobiliary disorders	1 (0.5)	0	1 (0.2)
Hepatic function abnormal	1 (0.5)	0	1 (0.2)

Abbreviations: N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Similarly, in the ocular category, a higher proportion of TEAEs were of mild (114 [26.5%] subjects) or moderate (45 [10.4%] subjects) intensity (ALT-L9-03 CSR). Severe TEAEs were reported in 2 (0.9%) subjects in the ALT-L9 group and in 4 (1.9%) subjects in the Eylea group.

The most common severe TEAE in the ocular category was endophthalmitis (1 [0.5%] subject in the ALT-L9 group and 2 [0.9%] subjects in the Eylea group. A summary of severe TEAEs by SOC and PT for the ocular category is presented in Table 21.

Table 21. Severe treatment-emergent adverse events by system organ class and preferred term for category ocular (safety analysis set)

SOC PT	ALT-L9 (N=216) n (%)	Eylea (N=215) n (%)	Overall (N=431) n (%)
At least 1 severe TEAE	2 (0.9)	4 (1.9)	6 (1.4)
Eye disorders	2 (0.9)	2 (0.9)	4 (0.9)
Cataract	2 (0.9)	0	2 (0.5)
Retinal pigment epithelial tear	0	1 (0.5)	1 (0.2)
Retinal haemorrhage	0	1 (0.5)	1 (0.2)
Infections and infestations	1 (0.5)	2 (0.9)	3 (0.7)
Endophthalmitis	1 (0.5)	2 (0.9)	3 (0.7)

Abbreviations: N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. A TEAE is defined as any event not present before the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment. If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
Source: Table 14.3.1.2.1.2

RELATEDNESS

Overall, the proportion of subjects with treatment-related TEAEs was low (less than 1.5% subjects) in both the treatment groups. The most common treatment-related TEAE was retinal pigment epithelial tear, reported in 2 subjects overall (1 subject in each treatment group); all other treatment-related TEAEs were reported in 1 subject each in either the ALT-09 or the Eylea group. No ocular treatment-related TEAE was reported in the fellow eye.

In the systemic category, treatment-related TEAEs were not reported in any subject in the ALT-L9 group. A total of 2 subjects in the Eylea group reported treatment-related TEAEs.

All treatment-related TEAEs are summarised in Table 22 below.

Table 22. Study ALT-L9-03: treatment-related treatment-emergent adverse events by category, system organ class and preferred term (safety analysis set)

SOC PT	ALT-L9 (N=216) n (%) e	Eylea (N=215) n (%) e	Overall (N=431) n (%) e
Category: Systemic			
At least 1 treatment-related TEAE	0	2 (0.9) 3	2 (0.5) 3
Nervous system disorders	0	2 (0.9) 3	2 (0.5) 3
Thrombotic cerebral infarction	0	1 (0.5) 2	1 (0.2) 2
Ischaemic stroke	0	1 (0.5) 1	1 (0.2) 1
Category[a]: Ocular			
At least 1 treatment-related TEAE	3 (1.4) 3	3 (1.4) 5	6 (1.4) 8
Eye disorders	3 (1.4) 3	2 (0.9) 2	5 (1.2) 5
Retinal pigment epithelial tear	1 (0.5) 1	1 (0.5) 1	2 (0.5) 2
Anterior chamber cell	0	1 (0.5) 1	1 (0.2) 1
Cataract	1 (0.5) 1	0	1 (0.2) 1
Retinal haemorrhage	1 (0.5) 1	0	1 (0.2) 1
Investigations	0	1 (0.5) 3	1 (0.2) 3
Intraocular pressure increased	0	1 (0.5) 3	1 (0.2) 3
Category[a]: Ocular – Study Eye			
At least 1 treatment-related TEAE	3 (1.4) 3	3 (1.4) 5	6 (1.4) 8
Eye disorders	3 (1.4) 3	2 (0.9) 2	5 (1.2) 5
Retinal pigment epithelial tear	1 (0.5) 1	1 (0.5) 1	2 (0.5) 2
Anterior chamber cell	0	1 (0.5) 1	1 (0.2) 1
Cataract	1 (0.5) 1	0	1 (0.2) 1
Retinal haemorrhage	1 (0.5) 1	0	1 (0.2) 1
Investigations	0	1 (0.5) 3	1 (0.2) 3
Intraocular pressure increased	0	1 (0.5) 3	1 (0.2) 3
Category[a]: Ocular – Fellow Eye			
None	-	-	-

Abbreviations: e, number of events; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; OU, Oculus Uterque; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
a. Events recorded as OU were counted separately under the study eye and fellow eye.
Source: Table 14.3.1.2.3.1

ALT-L9-01

Overall, 17 AEs were reported in 8 (28.57%) subjects. The incidence of AEs was higher in the control group (14 AEs in 6 [42.86%] subjects) than in the study group (3 AEs in 2 [14.29%] subjects).

A summary of all AEs is presented in Table 23 below.

Table 23. Overall adverse events (safety set)

	Study Group (N=14)		Control Group (N=14)		Total (N=28)	
Item	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
AEs	2 (14.29)	3	6 (42.86)	14	8 (28.57)	17
95% Confidence interval	(1.78, 42.81)		(17.66, 71.14)		(13.22, 48.67)	
p-value			0.2087			
ADRs	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
95% Confidence interval	(0.00, 23.16)		(0.00, 23.16)		(0.00, 12.34)	
p-value			NC			
SAEs	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
95% Confidence interval	(0.00, 23.16)		(0.18, 33.87)		(0.09, 18.35)	
p-value			1.0000			

Abbreviations: AE = adverse event; E = number of events; N = number of subjects; n = number of subjects with an event; NC = not calculated; SAE = serious adverse event; ADR = adverse drug reaction.
Treatment group: Study Group = ALT-L9 (Aflibercept), Control Group = EYLEA injection
Percentage was calculated using the number of subjects treated with each group.
P-values were calculated using Fisher's exact test.
Source: ALT-L9-01 CSR Table 18.

All AEs reported in the **study eye** occurred in subjects in the control group (6 AEs in 4 [28.57%] subjects). One SAE (glaucoma) in the study eye was also reported for one subject in the control group. For the study eye, 1 AE was reported as Grade 3 (severe or medically significant but not immediately life-threatening), and 1 AE was reported as Grade 4 (life-threatening consequences) in severity, the other study eye AEs were Grade 1 (asymptomatic or mild symptoms; no limitation in activities of daily living) or Grade 2 (limiting or affecting activities of daily living). None of these AEs were considered to be related to study treatment by the Investigator. They are summarised in Table 24 below.

Table 24. Summary of adverse events in the study eye (safety set)

Classification	Study Group (N=14) n (%)	E	Control Group (N=14) n (%)	E	Total (N=28) n (%)	E
AEs	0 (0.00)	0	4 (28.57)	6	4 (14.29)	6
SAEs	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Severity						
Grade 1	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Grade 2	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Grade 3	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Grade 4	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Relationship to the IP						
Not related	0 (0.00)	0	4 (28.57)	6	4 (14.29)	6
Action taken with the IP						
Dose not changed	0 (0.00)	0	2 (14.29)	4	2 (7.14)	4
Not applicable	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Treatments provided for AEs						
Medication treatment performed	0 (0.00)	0	3 (21.43)	3	3 (10.71)	3
Non-medication treatment performed	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Medication/non-medication treatment not performed	0 (0.00)	0	1 (7.14)	2	1 (3.57)	2
Outcome of AEs						
Recovered (Resolved)	0 (0.00)	0	4 (28.57)	4	4 (14.29)	4
Recovering (Resolving)	0 (0.00)	0	1 (7.14)	2	1 (3.57)	2

Abbreviations: AE = adverse event; E = number of events; IP = investigational product; N = number of subjects; SAE = serious adverse event.
Treatment group: Study Group = ALT-L9 (Aflibercept), Control Group = EYLEA injection
Source: ALT-L9-01 CSR Table 22.

Table 25. Incidence of adverse events per SOC in the study eye (safety set)

System Organ Class Preferred Terms	Study Group (N=14) n (%)	E	Control Group (N=14) n (%)	E	Total (N=28) n (%)	E
AEs in the study eye	0 (0.00)	0	4 (28.57)	6	4 (14.29)	6
p-value		0.0978				
Eye disorders	0 (0.00)	0	2 (14.29)	4	2 (7.14)	4
Dry eye	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Visual impairment	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Corneal erosion	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Glaucoma	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Infections and infestations	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Hordeolum	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Conjunctivitis	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1

Abbreviations: AE = adverse event; E = number of events; N = number of subjects; PT = preferred term; SOC = system organ class.
Treatment group: Study Group = ALT-L9 (Aflibercept), Control Group = EYLEA injection
Events are coded by SOC and PT of Medical Dictionary for Regulatory Activities (MedDRA).
One subject could be counted for more than one event.
P-value was calculated using Fisher's exact test.
Source: ALT-L9-01 CSR Table 26.

All AEs reported in the **fellow eye** occurred in subjects in the control group (4 AEs in 4 [28.57%] subjects); all were Grade 1 or 2 in severity. All AEs in the fellow eye were considered not related to study treatment by the Investigator and are summarised in Table 26 and Table 27 below.

Table 26. Summary of adverse events in the fellow eye (safety set)

	Study Group (N=14)		Control Group (N=14)		Total (N=28)	
Classification	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
AEs	0 (0.00)	0	4 (28.57)	4	4 (14.29)	4
SAEs	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Severity						
Grade 1	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Grade 2	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Relationship to the IP						
Not related	0 (0.00)	0	4 (28.57)	4	4 (14.29)	4
Action taken with the IP						
Dose not changed	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Not applicable	0 (0.00)	0	2 (14.29)	2	2 (7.14)	2
Treatments provided for AEs						
Medication treatment performed	0 (0.00)	0	4 (28.57)	4	4 (14.29)	4
Outcome of AEs						
Not recovered (not resolved)	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Recovered (Resolved)	0 (0.00)	0	3 (21.43)	3	3 (10.71)	3

Abbreviations: AE = adverse event; E = number of events; IP = investigational product; N = number of subjects; SAE = serious adverse event.
Treatment group: Study Group = ALT-L9 (Aflibercept), Control Group = EYLEA injection
Source: ALT-L9-01 CSR Table 23.

Table 27. Incidence of adverse events per SOC in the fellow eye (safety set)

System Organ Class Preferred Terms	Study Group (N=14)		Control Group (N=14)		Total (N=28)	
	n (%)	**E**	**n (%)**	**E**	**n (%)**	**E**
AEs in the fellow eye	0 (0.00)	0	4 (28.57)	4	4 (14.29)	4
p-value		0.0978				
Eye disorders	0 (0.00)	0	3 (21.43)	3	3 (10.71)	3
Dry eye	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Neovascular age-related macular degeneration	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Blepharitis	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Infections and infestations	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Conjunctivitis	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1

Abbreviations: AE = adverse event; E = number of events; N = number of subjects; PT = preferred term; SOC = system organ class.
Treatment group: Study Group = ALT-L9 (Aflibercept), Control Group = EYLEA injection
Events are coded by SOC and PT of Medical Dictionary for Regulatory Activities (MedDRA).
One subject could be counted for more than one event.
P-value was calculated using Fisher's exact test.
Source: ALT-L9-01 CSR Table 27.

A total of 7 AEs that were **non-ocular** were reported in 4 (14.29%) subjects: 3 AEs in 2 (14.29%) subjects in the study group and 4 AEs in 2 (14.29%) subjects in the control group. All non-ocular AEs were Grade 1 and 2 in severity and were not considered to be related to study treatment by the Investigator. They are summarised in Table 28 below.

Table 28. Incidence of adverse events (other) per SOC (safety set)

System Organ Class Preferred Terms	Study Group (N=14)		Control Group (N=14)		Total (N=28)	
	n (%)	E	n (%)	E	n (%)	E
Other AEs	2 (14.29)	3	2 (14.29)	4	4 (14.29)	7
p-value			1.0000			
Skin and subcutaneous tissue disorders	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Eczema	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Reproductive system and breast disorders	1 (7.14)	1	0 (0.00)	0	1 (3.57)	1
Scrotal dermatitis	1 (7.14)	1	0 (0.00)	0	1 (3.57)	1
Musculoskeletal and connective tissue disorders	1 (7.14)	1	0 (0.00)	0	1 (3.57)	1
Temporomandibular joint syndrome	1 (7.14)	1	0 (0.00)	0	1 (3.57)	1
Immune system disorders	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Drug hypersensitivity	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Infections and infestations	1 (7.14)	1	0 (0.00)	0	1 (3.57)	1
Periodontitis	1 (7.14)	1	0 (0.00)	0	1 (3.57)	1
Nervous system disorders	0 (0.00)	0	1 (7.14)	2	1 (3.57)	2
Ataxia	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1
Dizziness	0 (0.00)	0	1 (7.14)	1	1 (3.57)	1

Abbreviations: AE = adverse event; E = number of events; N = number of subjects; PT = preferred term; SOC = system organ class.
Treatment group: Study Group = ALT-L9 (Aflibercept), Control Group = EYLEA injection
Events are coded by SOC and PT of Medical Dictionary for Regulatory Activities (MedDRA).
One subject could be counted for more than one event.
P-value was calculated using Fisher's exact test.
Source: ALT-L9-01 CSR Table 28.

2.4.8.3. Serious adverse event/deaths/other significant events

ALT-L9-03

AESIs

The following AESIs were defined for close monitoring, reporting (by SOC and PT) and analysis:

- Arterial thromboembolic events: Arterial thromboembolic events were defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause) according to the Antiplatelet Trialists' Collaboration.
- Non-ocular haemorrhages
- All AEs related to IVT injection-related reactions, including but not limited to endophthalmitis, increases in IOP, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. AEs with a "Related" result for "Relationship to Intravitreal Injection Procedure" were considered as ISRs.

Overall, AESIs were reported in a higher proportion of subjects in the Eylea group (3.3% in the systemic category and 7.0% in the ocular category) compared with the ALT-L9 group (0.9% in the systemic category and 5.1% in the ocular category), for both the systemic and ocular categories.

The most common AESI in the systemic category was ischaemic stroke, reported in 1 (0.5%) subject in the ALT-L9 group and 3 (1.4%) subjects in the Eylea group. The most common AESI in the ocular category was intraocular pressure increased, reported in 3 (1.4%) subjects in each treatment group.

AESIs in the **systemic** and **ocular** categories are presented below (Table 29). All ocular AESIs were reported for the **study eye**.

Table 29. Adverse events of special interest by category, system organ class, and preferred term (safety analysis set)

Category [1]: Systemic

System Organ Class (SOC) Preferred Term (PT)	ALT-L9 (N=216) n (%) e	Eylea* (N=215) n (%) e	Overall (N=431) n (%) e
At Least One AESI	2 (0.9) 2	7 (3.3) 8	9 (2.1) 10
Nervous system disorders	2 (0.9) 2	4 (1.9) 5	6 (1.4) 7
Ischaemic stroke	1 (0.5) 1	3 (1.4) 3	4 (0.9) 4
Thrombotic cerebral infarction	0	1 (0.5) 2	1 (0.2) 2
Haemorrhage intracranial	1 (0.5) 1	0	1 (0.2) 1
Gastrointestinal disorders	0	2 (0.9) 2	2 (0.5) 2
Gastric ulcer haemorrhage	0	1 (0.5) 1	1 (0.2) 1
Intestinal haemorrhage	0	1 (0.5) 1	1 (0.2) 1
Cardiac disorders	0	1 (0.5) 1	1 (0.2) 1
Acute myocardial infarction	0	1 (0.5) 1	1 (0.2) 1

Category [1]: Ocular

System Organ Class (SOC) Preferred Term (PT)	ALT-L9 (N=216) n (%) e	Eylea* (N=215) n (%) e	Overall (N=431) n (%) e
At Least One AESI	11 (5.1) 14	15 (7.0) 18	26 (6.0) 32
Eye disorders	7 (3.2) 7	10 (4.7) 10	17 (3.9) 17
Conjunctival haemorrhage	1 (0.5) 1	4 (1.9) 4	5 (1.2) 5
Vitreous haemorrhage	2 (0.9) 2	0	2 (0.5) 2
Anterior chamber cell	0	1 (0.5) 1	1 (0.2) 1
Blindness	0	1 (0.5) 1	1 (0.2) 1
Conjunctival suffusion	1 (0.5) 1	0	1 (0.2) 1
Eye irritation	1 (0.5) 1	0	1 (0.2) 1
Foreign body sensation in eyes	1 (0.5) 1	0	1 (0.2) 1
Lacrimation increased	0	1 (0.5) 1	1 (0.2) 1
Punctate keratitis	0	1 (0.5) 1	1 (0.2) 1
Retinal pigment epithelial tear	1 (0.5) 1	0	1 (0.2) 1
Retinoschisis	0	1 (0.5) 1	1 (0.2) 1
Vitreous floaters	0	1 (0.5) 1	1 (0.2) 1
Investigations	3 (1.4) 6	3 (1.4) 5	6 (1.4) 11
Intraocular pressure increased	3 (1.4) 6	3 (1.4) 5	6 (1.4) 11
Infections and infestations	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Endophthalmitis	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Injury, poisoning and procedural complications	0	1 (0.5) 1	1 (0.2) 1
Injury of conjunctiva	0	1 (0.5) 1	1 (0.2) 1

e = number of events; N = Number of subjects in Safety Analysis Set for each treatment group; n = number of subjects with available data;
Percentage is calculated as n/N*100.
MedDRA (v 26.1) coding dictionary applied.
If a subject experienced more than 1 event in a given SOC that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT that subject is counted only once for that PT.
The AESIs included arterial thromboembolic events, nonocular hemorrhages, and all AEs related to IVT injection-related reactions.
[1] Events recorded as OU (Oculus Uterque) are counted separately under the study eye and fellow eye.
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ISRs

AEs with a "Related" result for "Relationship to Intravitreal Injection Procedure" were considered as ISRs.

The proportion of subjects who reported at least 1 ISR was higher in the Eylea group (7.0%) compared with the ALT-L9 group (5.1%). The most common ISR was intraocular pressure increased, reported in 6 (1.4%) subjects overall (3 [1.4%] subjects in each treatment group), followed by TEAEs of conjunctival haemorrhage which was reported in 5 (1.2%) subjects overall (1 [0.5%] subject in the ALT-L9 group and 4 [1.9%] subjects in the Eylea group), endophthalmitis which was reported in 3 (0.7%) subjects overall (1 [0.5%] subject in the ALT-L9 group and 2 [0.9%] subjects in the Eylea group), and vitreous haemorrhage which was reported in 2 (0.5%) subjects overall (both in the ALT-L9 group). See Table 30 below of reported ISRs.

Table 30. Injection-site reactions by system organ class and preferred term (safety analysis set)

SOC PT	ALT-L9 (N=216) n (%) e	Eylea (N=215) n (%) e	Overall (N=431) n (%) e
At least 1 injection-site reaction	11 (5.1) 14	15 (7.0) 18	26 (6.0) 32
Eye disorders	7 (3.2) 7	10 (4.7) 10	17 (3.9) 17
Conjunctival haemorrhage	1 (0.5) 1	4 (1.9) 4	5 (1.2) 5
Vitreous haemorrhage	2 (0.9) 2	0	2 (0.5) 2
Anterior chamber cell	0	1 (0.5) 1	1 (0.2) 1
Blindness	0	1 (0.5) 1	1 (0.2) 1
Conjunctival suffusion	1 (0.5) 1	0	1 (0.2) 1
Eye irritation	1 (0.5) 1	0	1 (0.2) 1
Foreign body sensation in eyes	1 (0.5) 1	0	1 (0.2) 1
Lacrimation increased	0	1 (0.5) 1	1 (0.2) 1
Punctate keratitis	0	1 (0.5) 1	1 (0.2) 1
Retinal pigment epithelial tear	1 (0.5) 1	0	1 (0.2) 1
Retinoschisis	0	1 (0.5) 1	1 (0.2) 1
Vitreous floaters	0	1 (0.5) 1	1 (0.2) 1
Investigations	3 (1.4) 6	3 (1.4) 5	6 (1.4) 11
Intraocular pressure increased	3 (1.4) 6	3 (1.4) 5	6 (1.4) 11
Infections and infestations	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Endophthalmitis	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Injury, poisoning and procedural complications	0	1 (0.5) 1	1 (0.2) 1
Injury of conjunctiva	0	1 (0.5) 1	1 (0.2) 1

Abbreviations: e, number of events; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; PT, preferred term; SOC, system organ class.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. An adverse event with a "Related" result in "Relationship to Intravitreal Injection Procedure" was considered as an injection-site reaction. If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
Source: Table 14.3.1.2.5

During the study, SAEs of endophthalmitis were reported for 3 subjects. The study treatment was administered to the subjects on the same date. All 3 subjects were hospitalised, and the study drug was discontinued because of the SAEs. The SAEs were considered not related to the study drug and were reported as a quality issue.

This issue was considered as "Critical-reportable noncompliance" with significant impact to subject safety within the clinical research quality system of the CRO since the 3 subjects were hospitalised because of the SAE related to the IVT injection procedure. The site procedures were reviewed, and a root cause analysis and relevant preventive actions were performed.

The site confirmed that all 15 subjects who had received an IVT injection on the same day had been contacted and no subject apart from the 3 subjects listed above were affected by this issue. The study drug administration was kept on hold and visits were delayed within the allowed window by the site. According to internal investigation performed by the site, all procedures were followed per the standard guidelines and the root cause was considered to be seasonal flu infecting the subjects while sitting together in the waiting room.

SERIOUS ADVERSE EVENTS

In the **systemic category**, the proportion of subjects who reported SAEs was comparable between the ALT-L9 group (25 subjects; 11.6%%) and the Eylea group (25 subjects; 11.6%). The most common SAE in the systemic category was ischaemic stroke, reported in 1 (0.5%) subject in the ALT-L9 group and 2 (0.9%) subjects in the Eylea group.

In the **ocular category**, the proportion of subjects who reported SAEs was comparable between the treatment groups. The SAEs reported in the ocular category were temporary blindness (1 (0.5%) subject in the Eylea group) and endophthalmitis (1 (0.5%) subject in the ALT-L9 group and 2 (0.9%) subjects in the Eylea group).

The 3 cases of endophthalmitis occurred in 3 subjects which all received an IVT application of the study drug on the same day at the same site. In all 3 subjects, study drug was discontinued because of the event. The event was considered related to the study procedure and unrelated to the study drug.

Most of the SAEs were reported in 1 subject each in either treatment group. SAEs reported in >1 subject in any treatment group are presented below (Table 31).

The applicant has provided case narratives for all reported SAEs.

Table 31. Serious adverse events by category, system organ class, and preferred term (safety analysis set)

SOC PT	ALT-L9 (N=216) n (%) e	Eylea (N=215) n (%) e	Overall (N=431) n (%) e
Category: Systemic[a]			
At least 1 SAE	25 (11.6) 29	25 (11.6) 31	50 (11.6) 60
Nervous system disorders	2 (0.9) 2	7 (3.3) 7	9 (2.1) 9
Ischaemic stroke	1 (0.5) 1	3 (1.4) 3	4 (0.9) 4
Infections and infestations	7 (3.2) 7	0	7 (1.6) 7
COVID-19	2 (0.9) 2	0	2 (0.5) 2
Category: Ocular			
At least 1 SAE	1 (0.5) 1	3 (1.4) 3	4 (0.9) 4
Infections and infestations	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Endophthalmitis	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Eye disorders	0	1 (0.5) 1	1 (0.2) 1
Blindness	0	1 (0.5) 1	1 (0.2) 1

Abbreviations: e, number of events; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; PT, preferred term; SAE, serious adverse event; SOC, system organ class.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
a. For the systemic category, only the most common SAEs (reported for >1 subject in either treatment group) are presented.
Source: Table 14.3.1.2.2.1

SERIOUS ADVERSE REACTIONS

In the systemic category, 2 SAEs (an SAE of thrombotic cerebral infarction for one subject and an SAE of ischaemic stroke for one subject) reported in the Eylea group were considered related to the study drug. Refer to section 3.3.7.2 (Relatedness) for summary of case narratives.

There were no treatment-related SAEs in the ocular category.

DEATHS

One subject was lost to follow-up from the Week 32 (Day 229) because of the subject´s death on Study Day 330 (serious TEAE of glioma).

The investigator assessed the SAE of glioma as unrelated to study drug, intravitreal injection, and study procedure. The alternate causality was reported as oncology incidence for the event of glioma.

OTHER SIGNIFICANT ADVERSE EVENTS

None of the events identified by the Risk Management Plan for ALT-L9 as important identified risks were observed as common TEAEs in Study ALT-L9-03, except for cataract, reported for 8 (3.7%) and 4 (1.9%) subjects in the ALT-L9 and Eylea groups, respectively. Episodes of endophthalmitis, eye inflammation, IOP increased, and retinal pigment epithelial tears were reported for one or both

treatment groups. Although uncommon, endophthalmitis was reported as an SAE for 1 (0.5%) and 2 (0.9%) subjects in the ALT-L9 and Eylea groups, respectively.

Retinal pigment epithelial tear was reported as a treatment-related TEAE for 1 (0.5%) subject in each of the ALT-L9 and Eylea groups, cataract was reported as a treatment-related TEAE for 1 (0.5%) subject in ALT-L9 group, and intraocular pressure increased was reported as a treatment-related TEAE for 1 (0.5%) subject in the Eylea group.

ALT-L9-01

AESIs

AESIs were not defined for Study ALT-L9-01. Selected AEs were identified as targeted AEs that required monitoring for the indication that were subject to the safety evaluation following IP administration:

- Occurrence of ocular inflammation assessed as Summed Ocular Inflammation Score (SOIS) of 4+ or higher
- Ocular inflammation assessed as SOIS of 2 or 3+ that failed to reduce to SOIS of 1+ or lower within 30 days from the date of onset
- Vision loss that exceeded 15 letters compared to BCVA evaluation at baseline prior to IP administration
- Sustained (exceeded 15 minutes) decline in light perception ability due to an increase of IOP
- IOP >20 mmHg and failed to return to the baseline IOP measured prior to IP administration within 7 days from the date of onset
- Occurrence of a new retinal tear or detachment

One targeted AE occurred in one subject in the Eylea group (in the **study eye**). This was an AE of vision decreased (categorised as 'vision loss that exceeded 15 letters compared to Best-Corrected Visual Acuity evaluation at baseline prior to IP administration') that occurred at Week 4. This AE was Grade 4 in severity and was assessed by the Investigator as not related to the study treatment. This AE had an outcome of 'Recovering (Resolving)'.

SERIOUS ADVERSE EVENTS

One (7.14%) subject in the control group experienced an SAE of glaucoma (verbatim term: 'aggravation of glaucoma') in the **study eye**. This SAE was considered Grade 3 in severity, and it was assessed as not related to study treatment by the Investigator. The study treatment dose was not changed, and no medication or treatment was provided in response to this SAE, which had an outcome of 'Recovering (Resolving)'.

DEATHS

No subjects died during this study.

2.4.8.4. Laboratory findings

ALT-L9-03

Clinical laboratory evaluations

Laboratory values and changes from baseline were summarised with descriptive statistics for haematology, chemistry, and urinalysis parameters. Overall, no significant trend was observed for laboratory parameters. No notable differences were observed between the treatment groups.

Laboratory abnormalities considered as SAEs were reported for 2 subjects (blood loss anaemia, anaemia). Both events were reported in the Elyea group, were severe in intensity, and were considered unrelated to the study drug, injection procedure, and the study procedure.

Vital signs

No clinically significant trend was observed in any treatment groups and results were comparable between both the treatment groups for vital signs.

Shifts from normal at baseline to abnormal clinically significant vital sign parameters at any post-baseline visit were reported as AEs for 11 subjects, 5 subjects in the ALT-L9 group and 6 subjects in the Eylea group. None was considered related to the study treatment.

Physical examination

No clinically significant trend was observed in any treatment groups and results were comparable between both the treatment groups for physical examination.

Ophthalmological examination

No clinically significant trend was observed in any treatment groups and results were comparable between both the treatment groups for ophthalmic examination (dilated fundus examination, slit-lamp examination).

IOP was comparable between the treatment groups at baseline and at all visits (pre-injection and post-injection).

ALT-L9-01

Clinical laboratory evaluations

For haematology, blood chemistry, blood coagulation and urinalysis, the difference in some parameters results between the study and control groups and between subjects within the same group were statistically significant. However, only one clinically significant value was observed, a creatine kinase value at Week 16 in the ALT-L9 arm. This value was not recorded as an AE as it was collected 28 days after the last dose of study treatment.

Vital signs

There were no statistically significant differences observed within and between treatment groups for vital signs assessments other than that of a change in mean diastolic blood pressure between baseline and Weeks 4 and 16 in subjects in the Eylea group.

Ophthalmological examination

Evaluation of slit lamp microscopy, fundoscopy, tonometry (IOP), and fundus photography revealed no significant differences at all time points and in both the study and control groups.

2.4.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.4.8.6. Safety in special populations

Not applicable.

2.4.8.7. Immunological events

Refer to section Pharmacodynamics.

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

Not applicable.

2.4.8.9. Discontinuation due to adverse events

ALT-L9-03

TEAEs resulting in study discontinuation are listed in Table 32 below.

Table 32. Treatment-emergent adverse events leading to study treatment discontinuation by category, system organ class, and preferred term (safety analysis set)

SOC PT	ALT-L9 (N=216) n (%) e	Eylea (N=215) n (%) e	Overall (N=431) n (%) e
Category: Systemic			
At least 1 TEAE leading to study treatment discontinuation	2 (0.9) 2	7 (3.3) 8	9 (2.1) 10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5) 1	3 (1.4) 3	4 (0.9) 4
Acute myeloid leukaemia	1 (0.5) 1	0	1 (0.2) 1
Lung adenocarcinoma	0	1 (0.5) 1	1 (0.2) 1
Lung cancer metastatic	0	1 (0.5) 1	1 (0.2) 1
Prostate cancer	0	1 (0.5) 1	1 (0.2) 1
Nervous system disorders	0	3 (1.4) 4	3 (0.7) 4
Ischaemic stroke	0	2 (0.9) 2	2 (0.5) 2
Thrombotic cerebral infarction	0	1 (0.5) 2	1 (0.2) 2
Gastrointestinal disorders	1 (0.5) 1	0	1 (0.2) 1
Pancreatitis acute	1 (0.5) 1	0	1 (0.2) 1
Skin and subcutaneous tissue disorders	0	1 (0.5) 1	1 (0.2) 1
Pemphigoid	0	1 (0.5) 1	1 (0.2) 1
Category: Ocular			
At least 1 TEAE leading to study treatment discontinuation	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Infections and infestations	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3
Endophthalmitis	1 (0.5) 1	2 (0.9) 2	3 (0.7) 3

Abbreviations: e, number of events; N, number of subjects in the Safety Analysis Set for each treatment group; n, number of subjects with available data; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Notes: Percentage was calculated as n/N × 100. Medical Dictionary for Regulatory Activities (Version 26.1) coding dictionary was applied. A TEAE is defined as any event not present before the initiation of the study treatment or any event already present that worsens in either intensity or frequency following exposure to the study treatment. If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT.
Source: Table 14.3.1.2.4.2

The proportion of subjects who discontinued the study treatment because of a TEAE was comparable between the treatment groups for the ocular category (0.5% for the ALT-L9 group and 0.9% for the Eylea group) and was higher in the Eylea group (3.3%) compared with the ALT-L9 group (0.9%) for the systemic category.

In the ocular category, endophthalmitis was reported in 1 (0.5%) subject in the ALT-L9 group and in 2 (0.9%) subjects in the Eylea group, leading to study drug discontinuation. In the systemic category, ischaemic stroke was reported in 2 (0.9%) subjects in the Eylea group, leading to study drug discontinuation. all other TEAEs that led to study treatment discontinuation were reported in 1 subject each in either treatment group, including acute myeloid leukaemia, lung adenocarcinoma, lung cancer metastatic, prostate cancer, thrombotic cerebral infarction, pancreatitis acute, and pemphigoid.

The proportion of subjects who withdrew from the study because of a TEAE was comparable between both treatment groups for both the systemic category (1.4% and 2.8% for the ALT-L9 and Eylea groups, respectively) and ocular category (0.5% and 0.9% for the ALT-L9 and Eylea groups, respectively).

The most common TEAE leading to study withdrawal was endophthalmitis in the ocular category, reported for 1 (0.5%) subject in the ALT-L9 group and for 2 (0.9%) subjects in the Eylea group. All other TEAEs that led to study treatment discontinuation were reported for 1 subject each in either treatment group.

ALT-L9-01

No subject discontinued from this study.

2.4.8.10. Post marketing experience

Not applicable.

2.4.9. Discussion on clinical safety

Safety assessment

The safety assessment of the aflibercept biosimilar ALT-L9 was conducted by taking into account the known safety profile of the reference product Eylea (aflibercept (EU)). This is line with the overall concept of comparable safety evaluation for a similar biological medicinal product and thus acceptable.

The clinical safety assessment of ALT-L9 is based on comparative data derived from the supportive phase 1 (**ALT-L9-01**) and pivotal phase 3 (**ALT-L9-03**) studies.

Study ALT-L9-03 was conducted in Europe and Asia Pacific, including a total of 431 subjects diagnosed with nAMD who received 2 mg aflibercept (either ALT-L9 or EU-Eylea; 1:1 randomised) by IVT once every 4 weeks up to Week 8 and every 8 weeks thereafter (Weeks 16, 24, 32, 40 and 48). Study ALT-L9-01 was conducted in the Republic of Korea including 28 nAMD patients who received 2 mg aflibercept (either ALT-L9 or EU-Eylea; 1:1 randomised) by IVT once every 4 weeks for 8 weeks, for a total of 3 doses.

Safety in ALT-L9-03 was evaluated in accordance with EMA scientific advice with respect to frequency of assessments and pre-defined AESIs. Chosen safety parameters and respective examinations are considered to be sufficiently sensitive to enable detection of respective adverse events.

Whilst data from ALT-L9-01 are considered as part of the overall safety database, their value is considered limited, confounded by the enrolment of subjects that have been pre-treated with anti-VEGF medicines aflibercept, bevacizumab, and ranibizumab. It is noted that patients in the test arm had a larger median number of previous anti-VEGF administrations in the study eye compared to the reference arm (25 versus 17), which may be linked to the longer disease duration in these patients. Treatment-experienced patients represent a less sensitive study population and from a safety perspective, the assessment of immunogenicity and adverse event profile may be compromised. Data derived from ALT-L9-01 are nonetheless considered supportive in the overall comparability exercise, whilst data collected from the phase 3 study are considered pivotal due to that study's design (including a more sensitive study population [treatment naïve AMD patient], sample size, etc) and duration (48-week treatment).

Baseline data, including demographics, general disease characteristics, medical history, prior and concomitant medication for Study ALT-L9-03 are presented in section 2.4.5.2 of this report. Test and control arms were considered well balanced. A perceived imbalances between groups for the percentage of patients receiving anti-infectives agents as concomitant medications were discussed further by the applicant. It is agreed that observed imbalances do not signify any inherent differences in the safety profile of the two products.

In responses, the applicant has provided the full safety dataset for the study's 48-week treatment period and 4-week follow-up period in the final CSR. Data, additional to those presented in the interim CSR, were integrated into the full analysis, but differences between both dossier versions were clearly highlighted. Discrepant results between the interim and final CSRs were clarified by the applicant in responses (question raised under Clinical Efficacy).

Patient exposure

A total of 459 subjects have participated in one of the two clinical studies (ALT-L9-01 and ALT-L9-03), with 230 subjects having received at least one dose of the test product to date. Long term exposure data (48-week treatment) for 205 subjects were provided in the final CSR for ALT-L9-03.

In study ALT-L9-03, as reported in the final CSR, the mean number of weeks of exposure and injections were 46.8 and 7.8, respectively, in the ALT-L9 group and 46.7 and 7.8, respectively, in the Eylea group. Based on final analysis of study ALT-L9-03, a total of 26 subjects (6.0%) discontinued the study prematurely, including 12 patients (5.6%) in the ALT-L9 group and 14 (6.5%) in the Eylea group. Therefore, no relevant differences in the exposure to study treatment between the two treatment groups were observed.

In study ALT-L9-01, a total of 28 subjects were randomised (14 subjects per group). All 28 subjects completed study treatment for a total of 8 weeks and received all treatment doses (3 doses every 4 weeks). Therefore, between the two treatment groups, no relevant differences in exposure to the study treatment were observed.

Although, according to ICH E1 guideline on Population Exposure; The Extent of Population Exposure to Assess Clinical Safety [CPMP/ICH/375/95, 1995], 100 patients exposed for a minimum of one year is considered acceptable to be included as part of the safety data base; exposure of ~ 200 patients for a 48-week treatment period, followed by a 4-week follow-up period, is accepted. The provided safety database is considered sufficient to assess the comparability of common (≥1/100 to <1/10) and very common (≥1/10) adverse events. However, it is too small to inform on less frequently occurring adverse events. This approach is considered adequate for biosimilar development.

TEAEs (type, frequency, relatedness)

In the pivotal **Study ALT-L9-03**, in the systemic category, AEs were reported in 122 (56.5%) subjects in the ALT-L9 group and 118 (54.9%) subjects in the Eylea group. The overall reported number of AEs, TEAEs and treatment-related TEAEs were similar between both treatment arms, with no treatment-related TEAEs being reported in the test arm. Two subjects reported 3 treatment-related TEAEs in the reference arm. No imbalances of concern were observed in the type of TEAEs reported between treatment groups, with the most common TEAEs by PT being nasopharyngitis (11 [5.1%] subjects), COVID-19 (11 [5.1%] subjects), and hypertension [11 [5.1%] subjects) in the test arm, and nasopharyngitis (21 [9.8%] subjects), hypertension [10 [4.7%] subjects) and backpain [5 [2.3%] subjects) in the reference arm.

TEAEs in both arms were largely mild or moderate in intensity, with severe TEAEs being reported in 9 (4.2%) subjects in the test arm and in 13 (6.0%) subjects in the reference arm. The most common severe TEAE in the systemic category was ischaemic stroke, reported for 1 subject in each treatment group; all other severe TEAEs were reported for 1 subject in either treatment group.

In the ocular category, TEAEs were reported in 90 (41.7%) subjects in the ALT-L9 group and in 75 (34.9%) subjects in the Eylea group. The most reported ocular TEAE was nAMD in the fellow eye (23 [10.6%] subjects in the ALT-L9 group versus 13 [6.0%] subjects in the Eylea group). The most common TEAE in the study eye was visual acuity reduced, reported in 9 (4.2%) subjects in the ALT-L9 group and in 8 (3.7%) subjects in the Eylea group. Perceived imbalances between treatment arms with respect to the combined reporting for the study and fellow eye of TEAEs of 'neovascular age-related macular degeneration' and 'subretinal fluid' were adequately addressed by the applicant. It is agreed that observed imbalances do not reflect a meaningful difference in the safety profiles of ALT-L9 and Eylea.

In the ocular category, treatment-related TEAEs were reported for 3 subjects each in both the ALT-L9 group (retinal pigment epithelial tear, cataract, and retinal haemorrhage) and the Eylea group (retinal pigment epithelial tear, anterior chamber cell, 3 events of intraocular pressure increased in one subject). All these adverse events, except anterior chamber cell, are included as adverse reactions in the SmPC of Eylea. Even though anterior chamber cell is not included in the SmPC of Eylea, anterior chamber flare is, and both are markers of ocular inflammation.

The majority of TEAEs reported in the ocular category were mild to moderate in intensity, with severe TEAEs being reported in 2 (0.9%) subjects in the ALT-L9 group and in 4 (1.9%) subjects in the Eylea group. The most common severe TEAE in the ocular category was endophthalmitis (1 [0.5%] subject in the test arm and 2 [0.9%] subjects in the reference arm).

In Study ALT-L9-03, overall (systemic and ocular categories), there were no imbalances of concern noted between the test and reference arms with respect to the type, incidence, severity and relatedness of TEAEs reported. TEAEs were as per the known safety profile of Eylea. No new safety concerns were identified.

In the phase 1 supportive study, **ALT-L9-01**, there was a higher incidence of AEs reported in the reference arm (14 AEs in 6 [42.86%] subjects) than in the test arm (3 AEs in 2 [14.29%] subjects). All AEs reported in the study eye and fellow eye occurred in the control arm. None were considered related to the IP, and no particular AE was reported in more than one subject. Of the non-ocular AEs reported, none were considered related to the IP, and no one AE was reported in more than one subject. The majority of all AEs were considered Grade 1 or 2 in severity. One AE was reported as Grade 3 and one as Grade 4. Both occurred in the study eye of the reference arm.

Overall, with respect to safety data from ALT-L9-01, there were no imbalances of concern noted between the test and reference arms with respect to the type, incidence, severity and relatedness of

TEAEs reported. TEAEs were as per the known safety profile of Eylea. No new safety concerns were identified.

AESIs, SAEs, serious ADRs, deaths

For **Study ALT-L9-03**, AEs related to arterial thromboembolic events, non-ocular haemorrhage and IVT injection-related reactions were predefined as AESIs. Overall, AESIs were reported in a higher proportion of subjects in the Eylea group for both the systemic and ocular categories (3.3% and 7.0%, respectively) compared with the ALT-L9 group (0.9% and 5.1%, respectively). The most common AESI in the systemic category was ischaemic stroke, reported in 1 (0.5%) and 3 (1.4%) subjects in the ALT-L9 and Eylea groups, respectively. The most common AESI in the ocular category was intraocular pressure increased reported in 3 (1.4%) subjects in each treatment group. All ocular AESIs were reported in the study eye.

AEs that were considered related to the IVT procedure were categorised as ISRs, with increased intraocular pressure increased being the most reported: 6 (1.4%) subjects overall (3 subjects in each treatment group; 1.4%). This was followed by TEAEs of conjunctival haemorrhage reported for 5 (1.2%) subjects overall (1 (0.5%) subject in the ALT-L9 group and 4 (1.9%) subjects in the Eylea group), endophthalmitis reported for 3 (0.7%) subjects overall (1 (0.5%) subject in the ALT-L9 group and 2 (0.9%) subjects in the Eylea group), and vitreous haemorrhage reported for 2 (0.5%) subjects overall (both in the ALT-L9 group). Vitreous haemorrhage was, therefore, the only adverse event that occurred in a higher proportion in the test arm. This event is described as a common side effect in the product information of Eylea. All other ISRs were reported for 1 subject each in either treatment group.

The test and reference IPs were of differing presentations, a solution for injection in vial and solution for injection in a pre-filled syringe, respectively. The applicant provided adequate justification as to why the use of differing presentations in the study did not impact on the safety comparability exercise, supported by evidence of a low and comparable incidence of ISRs, including IOP increased, between treatment groups.

With respect to SAEs, in the systemic category, the proportion of subjects who reported SAEs was comparable between the ALT-L9 and the Eylea groups (25 [11.6%] subjects each). The most common SAE in the systemic category was ischaemic stroke (1 (0.5%) subject in the ALT-L9 group and 3 (1.4%) subjects in the Eylea group). In the ocular category, the proportion of subjects who reported SAEs was comparable between the treatment groups (ALT-L9: 0.5%, Eylea: 1.4%). The SAEs reported in the ocular category were temporary blindness (1 subject in the Eylea group) and endophthalmitis (1 subject in the ALT-L9 group and 2 subjects in the Eylea group).

The 3 cases of endophthalmitis occurred in 3 subjects which all received an IVT application of the study drug on the same day at the same site. In all 3 subjects, study treatment was discontinued because of the event. The event was considered related to the IVT injection procedure and unrelated to the study drug.

Two SAEs in the systemic category, ischaemic stroke in 1 subject and thrombotic cerebral infarction in another subject (both in the Eylea group), were considered related to study treatment.

There was one death reported. One subject randomised to the ALT-L9 group died due to a TEAE (glioma) after the study. This fatal event was not considered related to the study drug.

For **Study ALT-L9-01**, AESIs were not defined.” Targeted AEs”, however, were defined as those “requiring monitoring for the indication that were subject to the safety evaluation following IP administration”. One targeted AE was reported in one subject in the control group in the study eye.

This was an AE of vision decreased (categorised as 'vision loss that exceeded 15 letters compared to Best-Corrected Visual Acuity evaluation at baseline prior to IP administration') that occurred at Week 4. The AE was Grade 4 in severity and considered unrelated to the IP.

With respect to SAEs, one subject in the control group experienced an SAE of glaucoma in the study eye. The AE was Grade 3 in severity and considered unrelated to the IP.

There were no serious ADRs, or deaths reported in this study, whose results were overall supportive of the comparative safety profile of test and reference products.

Discontinuations due to adverse events

The proportion of subjects who discontinued the study treatment because of a TEAE was comparable between in the ocular category (ALT-L9: 0.5%, Eylea: 0.9%) and was higher in the Eylea group (3.3%) compared with the ALT-L9 group (0.9%). The most common TEAE leading to study treatment discontinuation was endophthalmitis in the ocular category, reported for 1 (0.5%) subject in the ALT-L9 group and in 2 (0.9%) subjects in the Eylea group.

With regard to the TEAEs of endophthalmitis, the 3 cases occurred in 3 subjects who received an IVT application of the study drug on the same day at the same site. In all 3 subjects, study drug was discontinued, and the patients were withdrawn from the study due to the event. An internal investigation was performed, and the root cause was seasonal flu infecting the subjects while sitting together in the waiting room. Therefore, the event was considered related to the study procedure and unrelated to the study drug. Preventive actions were implemented at the site and these events were reported as a quality issue.

In the systemic category, ischaemic stroke was reported in 2 (0.9%) subjects in the Eylea group; all other TEAEs that led to study treatment discontinuation were reported in 1 subject each in either treatment group.

The proportion of subjects who withdrew from the study because of a TEAE was comparable between the treatment groups for both the systemic category (1.4% for the ALT-L9 group and 2.8% for the Eylea group) and the ocular category (0.5% for the ALT-L9 group and 0.9% for the Eylea group).

No subject discontinued study treatment in Study **ALT-L9-01**.

Laboratory and other investigations.

In **Study ALT-L9-03**, the incidence of TEAEs relating to clinical laboratory evaluations, vital signs, physical and ophthalmological examination was low, with no notable imbalances observed between treatment groups. Any abnormalities of test results were reported as a TEAE if determined to be clinically significant by the investigator and are thus covered in the section on Adverse Events in this report. The same holds true for vital signs and related parameters. No new safety concerns were noted.

In **Study ALT-L9-01**, there were no notable differences observed between treatment groups with respect to clinical laboratory evaluations, vital signs, and ophthalmological examination. No new safety concerns were noted.

Overall, from a safety perspective (ocular and systemic), with consideration to the type, frequency, severity, and relatedness of reported TEAEs, the incidence of AESIs or targeted AEs, SAEs, SAEs considered related to the IP, AEs leading to study discontinuation, and deaths, no notable differences were observed between the profiles of the test and reference products.

2.4.10. Conclusions on the clinical safety

Based on the evaluation of safety datasets derived from the supportive Phase I study (Study ALT-L9-01) and pivotal Phase 3 study (Study ALT-L9-03), the overall safety profile of ALT-L9 is considered to be in line with the known safety profile of the reference product, Eylea. No new safety concerns have been identified.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 33. Summary of safety concerns

Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin)
Important potential risks	• Medication errors • Off-label use and misuse • Embryo-fetotoxicity
Missing information	• None

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Table 34. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaires are used for enhanced pharmacovigilance

	Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	monitoring of endophthalmitis/intraocular inflammation cases (see Annex 4). **Additional pharmacovigilance activities:** None
Intraocular inflammation	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaires are used for enhanced pharmacovigilance monitoring of endophthalmitis/intraocular inflammation cases (see Annex 4). **Additional pharmacovigilance activities:** None
Transient intraocular pressure increase	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet sections 2 and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** **Educational program:** Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Retinal pigment epithelial tears	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8 Package Leaflet sections 2 and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

	Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	
Cataract (especially of traumatic origin)	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Medication errors	**Routine risk minimisation measures:** SmPC sections 4.2 and 4.9 Package Leaflet section 1 and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Off-label use and misuse	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.6 Package Leaflet sections 1, 2, and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

	Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	
Embryo-fetotoxicity	**Routine risk minimisation measures:** SmPC sections 4.4, 4.6, and 5.3 Package Leaflet section 2 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eyluxvi must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video) and patient guide "Your guide to Eyluxvi" and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

2.5.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

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 Eylea. The bridging report submitted by the applicant has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Eyluxvi (aflibercept) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

The applicant has performed two clinical trials to support the development of the proposed biosimilar, a first-in-human phase I trial (ALT-L9-01) for safety and a pivotal phase III trial (ALT-L9-03).

ALT-L9 (aflibercept) has been developed for the same use as the reference medicinal product Eylea, with respect to intravitreal route of administration, posology, and therapeutic indications in adults. The applicant is not pursuing the indication of retinopathy of prematurity in preterm infants for ALT-L9 (aflibercept).

A comprehensive analytical exercise was performed to evaluate ALT-L9 similarity with EU-Eylea reference medicinal product in all relevant physical and chemical attributes and functional characteristics.

3.2. Results supporting biosimilarity

Quality

The attributes included in the comparative assessment cover the relevant attributes for a product of this nature and were analysed using a comprehensive set of orthogonal state-of-the–art analytical methods.

The statistical approach to setting the acceptance criteria for the high and medium risk attributes is endorsed. For lower ranked attributes the applicant used fewer batches and applied a qualitative approach. Overall, ALT-L9 was found to be highly similar to Eylea.

Efficacy

The primary endpoint of change from baseline in BVCA at week 8 was met for the pivotal trial, as were most of the related sensitivity analyses. Results for secondary endpoints of the change from baseline in BCVA at different timepoints, the proportion of subjects who gained or lost at least 5, 10 and 15 letters, the change from baseline in CST, sub or intraretinal fluids and the total size of CNV area were comparable across both treatment arms. The phase 1 trial provides some limited supportive data to the pivotal trial.

Safety

The safety profiles of the test and reference products are comparable with regards to reported TEAEs, their type, frequency, severity and relatedness. No notable imbalances of concern have been noted for ocular or systemic TEAEs. Reported TEAEs are in line with the known safety profile of the reference product and no new safety concerns were identified in either of the clinical studies.

There was one death reported in the test arm of the phase 3 study, but this was not considered related to the investigational product.

The proportion of participants withdrawing from the study due to an adverse event (ocular and systemic) were broadly similar.

Changes in mean values from baseline for haematology parameters, chemistry parameters, urinalysis and vital signs were comparable between the treatment groups.

Immunogenicity

ADA positive status was reported in patients in the phase 3 study only. The incidence of ADAs was generally low), and broadly in line with that expected for the reference product. Titres were low. There were no notable imbalances observed between treatment groups with respect to ADA and NAb incidence at any time point during the study.

3.3. Uncertainties and limitations about biosimilarity

The applicant has demonstrated biosimilarity of Eyluxvi to Eylea.

Efficacy

For one of the sensitivity analyses linked to the primary endpoint data, the 95% CI did not lie within the predefined margin of ±3.49 letters (LOCF for the primary estimand) and many of the subgroup analyses did not support bioequivalence**.** However, the overall results demonstrated bioequivalence between the test and the reference product.

3.4. Discussion on biosimilarity

A comprehensive analytical exercise was performed to evaluate ALT-L9 similarity with EU-Eylea reference medicinal product in all relevant physical and chemical attributes and functional characteristics.

Overall, the efficacy results can generally be considered as demonstrating bioequivalence between the test and the reference product.

Overall, the safety profiles for ALT-L9 and Eylea are comparable.

The immunogenicity profiles for ALT-L9 and Eylea are comparable.

3.5. Extrapolation of safety and efficacy

The pivotal study was conducted in subjects with neovascular age-related macular degeneration (nAMD). nAMD is one of the approved indications of Eylea 40 mg/mL solution for injection in a vial in the EU. Other approved indications include retinal vein occlusion (RVO), diabetic macular oedema (DME) and choroidal neovascularisation (CNV). Studies with the reference product demonstrated that the treatment effect of aflibercept was largest in patients with nAMD (comparison against placebo).

nAMD is therefore likely the most sensitive of the approved indications to detect any differences between the treatments in terms of clinical efficacy. The receptor and mechanism of action of aflibercept are the same across different ophthalmological indications approved for the reference product and aflibercept is directly delivered at its site of action. Since nAMD patients are generally considered a sensitive population for assessing similarity in clinical efficacy of aflibercept, it is agreed that since similarity for Eyluxvi is demonstrated in nAMD patients, the findings can be extrapolated to other indications approved for Eylea.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Eyluxvi is considered biosimilar to Eylea. 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 Eyluxvi is favourable in the following indication(s):

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),
- visual impairment due to diabetic macular oedema (DME) (see section 5.1),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

The MAH has agreed to provide EU educational material for Eyluxvi. Prior to launch and during the product's lifecycle in each Member State the MAH will agree the final educational material with the National Competent Authority.

The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Eyluxvi is marketed, ophthalmological clinics where Eyluxvi is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- Confirmation that the vial is for single use only
- The need to expel excess volume of the syringe before injecting Eyluxvi to avoid overdose
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eyluxvi

The patient information pack of the educational material includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Eyluxvi
- How to prepare for Eyluxvi treatment
- What are the steps following treatment with Eyluxvi
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract

- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eyluxvi