19 June 2025
EMA/CHMP/203339/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mynzepli

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006438/0000

Note

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

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

List of abbreviations

ACS	Abnormal, clinically significant
ADA	Anti-drug antibody
ADCC	Antibody-dependent Cellular Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse event
AESI	Adverse events of special interest
AH	Aqueous humor
ALT	alanine aminotransferase
AMD	Age-related macular degeneration
AR	Assessment Report
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BCVA	Best-corrected Visual Acuity
BDRM	Blinded Data Review Meeting
BMI	Body mass index
BP	Blood pressure
BRVO	Branch retinal vein occlusion
C1q	Complement component 1q
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence interval
CL	Clearance
Cmax	Maximum observed concentration
CNV	Choroidal neovascularization
COVID-19	Coronavirus Disease 2019
CRC	Central reading center
CRF	Case report form
CRO	Contract research organization
CRVO	Central retinal vein occlusion
CSR	Clinical Study Report
CST	Central subfield thickness
CTCAE	Common Terminology Criteria for Adverse Event
CTMS	Clinical trial management system
CV%	Coefficient of variation as a percent
DKMA	Danish Medicines Agency
DME	Diabetic macular edema
DP	Drug product
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
ENR	Entered Analysis Set
EOS	End of Study
EoT	End of Treatment
ERA	Environmental Risk Assessment

ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	Europe
FA	Fluorescein angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FcRn	Neonatal Fc receptor
FP	Fundus photography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IA	Interim Analysis
ICE	Intercurrent Events
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IOP	Intraocular Pressure
IWRS	Interactive Web Response System
LLoQ	Lower limit of quantification
LS	Least squares
IVT	Intravitreal Injection
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
N/A	Not applicable
NAb	Neutralizing antibody
OCT	Optical coherence tomography
OECD	Organisation for Economic Cooperation and Development
PD	Pharmacodynamic
PFS	Pre Filled Syringe
PlGF	Placental growth factor
PK	Pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PT	Preferred term
RND	Randomly Assigned to Study Treatment Analysis Set
ROP	Retinopathy of prematurity
RVO	Retinal vein occlusion
SA	Scientific Advice
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Standard Deviation
SE	Standard error
SOC	System organ class
SPR	Surface Plasmon Resonance
TEAE	Treatment-Emergent Adverse Event
TK	Toxicokinetic
Tmax	Time of maximum observed plasma concentration
ULM	upper limit of normal
US	United States
VA	Visual acuity

VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VH	Vitreous humor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Advanz Pharma Limited submitted on 29 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Mynzepli, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Mynzepli 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 and multiples

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

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 40mg/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

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/0000063900	*Linda Trauffler, Kerstin Wickström*
15 December 2022	EMA/SA/0000111491	*Kerstin Wickström, Juha Kolehmainen*

The applicant received scientific advice on the development of their aflibercept biosimilar for the treatment of neovascular (wet) age-related macular degeneration from the CHMP on 16 September 2021 (EMA/SA/0000063900). The scientific advice pertained to the following Quality, Non-Clinical, and Clinical aspects:

Quality •Approach to comparative analytical similarity exercise, panel of analytical methods, primary potency assay for release and stability testing, orthogonal method for analytical similarity assessment, panel of methods to be used for lot release.

Nonclinical •Adequacy of toxico-pharmacological development, design of in vivo safety study.

Toxico-Pharmacological and Clinical• Strategy and assay design to quantitate study drug and reference medicinal product in clinical samples, assay design for the detection of anti-drug antibodies, assay design for the detection of neutralizing anti-drug antibodies.

Clinical •Adequacy of clinical development strategy; design of randomized controlled trial in subjects with wet age-related macular degeneration to demonstrate similar efficacy, safety, immunogenicity and systemic PK of the study drug and the reference medicinal product: overall design, indication, primary and secondary endpoints, equivalence margin, statistical assumptions, duration of safety assessment, duration of immunogenicity assessment, submission plan for clinical study report; extrapolation to all indications of the reference medicinal product.

The applicant received scientific advice on the development of the biosimilar aflibercept (AVT06) for the same indications as the reference medicinal product Eylea i.e. neovascular age-related macular degeneration and visual impairment due to diabetic macular oedema (DME), choroidal neovascularisation (CNV) secondary to pathologic myopia (PM) and macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) from the CHMP on 15 December 2022 (EMA/SA/0000111491). The Scientific Advice pertained to the following Quality and Clinical aspects:

Quality.• stability analysis of Process Performance Qualification (PPQ) batches.

Clinical •timing of submission of safety data in a Marketing Authorisation Application (MAA).

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jean-Michel Race Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	29 July 2024
The procedure started on	15 August 2024

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 November 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	15 November 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	31 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP agreed on a list of outstanding issues in writing 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	4 June 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 Mynzepli on	19 June 2025

2. Scientific discussion

2.1. About the product

Mynzepli was developed as a biosimilar product to Eylea (INN: aflibercept; EMEA/H/C/002392) for intravitreal injection only (pharmaceutical form: vial and pre-filled syringe).

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 indications and posology proposed are the same as the reference medicinal product, with exception of Retinopathy of prematurity (ROP).

2.2. Quality aspects

2.2.1. Introduction

Mynzepli (AVT06 (aflibercept company code)) has been developed as biosimilar to Eylea (aflibercept) as reference product.

Mynzepli 40 mg/ml is presented as a sterile, preservative-free solution for intravitreal injection, containing 40 mg of aflibercept per 1 ml as active substance (AS).

Other ingredients are: L-histidine, L-histidine monohydrochloride monohydrate, trehalose dehydrate, poloxamer 188, and water for injections

The product is available in:

- a vial (type I glass) with a stopper (elastomeric bromobutyl rubber), and an 18 G filter needle. Each 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. Pack size of 1 vial + 1 filter needle.
- a pre-filled syringe (type I glass) marked with a dosing line, with a plunger stopper (elastomeric bromobutyl rubber) and a Luer lock adaptor with a tip cap (elastomeric rubber). Each pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept. Pack size of 1 pre-filled syringe

2.2.2. Active substance

2.2.2.1. General information

Aflibercept is a recombinant Fc fusion protein created by fusing the second Ig domain of human vascular endothelial growth factor receptor 1 (VEGFR1) with the third Ig domain of human VEGFR2, which is in turn fused to the constant region of human IgG1. This protein is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aflibercept acts as a soluble decoy

receptor that binds to multiple isoforms of human VEGF-A, VEGF-B and placental growth factor (PlGF), preventing it from interacting with its receptors (VEGFR-1 and VEGFR-2).

Structurally, aflibercept is a dimeric glycoprotein, with C-terminal lysine clipped polypeptide being the major form. All five putative N-glycosylation sites on each polypeptide chain predicted by the primary sequence can be occupied with carbohydrate and exhibit some degree of chain heterogeneity, including heterogeneity in terminal sialic acid residues.

Sufficient information regarding the nomenclature, structure, and general properties of aflibercept (AVT06) has been provided, including disulfide bonds and glycosylation sites, as well as brief description of the mechanism of action.

2.2.2.2. Manufacture, characterisation and process controls

Manufacturers

Name, address, and responsibilities of all manufacturers involved in manufacture and in-process control (IPC), quality control, and stability testing of the active substance as well as manufacturing and storage sites of cell banks listed in this section is sufficient.

All active substance manufacturing sites are GMP compliant.

Description of manufacturing process and process controls

The active substance of AVT06, i.e. aflibercept, is expressed in a CHO cell line. The process set-up consists of an upstream and downstream process as outlined in the relevant dossier section.

Manufacture of a batch starts from a single vial of the working cell bank (WCB). After thawing, cells are expanded under controlled conditions. The cells are expanded in a series of seed expansion steps from shake flasks, (scale single use bioreactor (SUB).

In the downstream process (DSP), the clarified harvest is purified using a series of purification steps. The purified material is formulated, filtered, and filled into AS containers and stored prior to further processing into finished product.

The applicant provided a description of the manufacturing process steps that is accompanied by flow charts and tables listing process and performance parameters with their classification (critical process parameters (CPP) or non-critical process parameter (nCPP)). Action limits for IPCs have been provided. In process-hold times are stated. The details of hold time studies have been provided. No reprocessing is foreseen in the manufacture of AVT06 active substance.

The manufacturing process is considered to be adequately described, and the different steps are sufficiently depicted.

Batch and Scale Definition

Definitions of batch and scale have been provided. Batch numbering system was adequately described.

Control of materials

Raw materials

The raw materials for the upstream and downstream process are described. Compendial materials are listed. For non-compendial materials, rrespective vendor’s Certificates of Analysis (CoAs) are provided.

The qualitative composition of the cultivation media has been included in the dossier. Cell culture media and buffers are described.

The microbial control of cell culture reagents is adequately defined in this section. Information on resins and filters used during downstream processing is considered sufficient. Sufficient information on resin cycles and the validation of the resin use cycles has been provided.

No raw materials of animal or human origin are used in the manufacturing process.

Cell substrate

AVT06 is expressed in a recombinant CHO cell line. The construction of the expression vector and its genetic elements are described in sufficient detail.

The source, history and generation of the cell substrate is sufficiently described and in accordance with the recommendations of ICH Q5B and ICH Q5D.

A two-tiered cell bank system was established. Vials of both MCB and WCB are stored in separate locations. Satisfactory protocols describing manufacture and qualification acceptance criteria of new WCBs and routine stability monitoring of MBC and WCB (with cell viability and viable cell density) are available.

Comprehensive testing of MCB and WCB in line with ICH Q5D was performed (identification, sterility, mycoplasma, and genetic stability). Brief descriptions of methods used for the characterisation of cell banks have been provided.

Control of critical steps and intermediates

The list of critical quality attributes (CQAs) has been provided as well as the list of IPCs. Sufficiently comprehensive criticality assessment was provided and overall criticality ranking is endorsed for individual quality attributes.

Overall, the submitted risk assessment identifies the relevant attributes of aflibercept AS and finished product (FP) and is deemed acceptable.

For IPCs, action limits or acceptance criteria are provided. The limits of these IPCs were defined based on development, manufacturing experience and process characterisation studies. The defined IPCs were tested in the process performance qualification (PPQ) studies and the details were presented.

The analytical methods for in-process controls are adequately described.

Hold times are defined at several AS manufacturing steps.

The information provided in this section is adequate and sufficient.

Process validation and/or evaluation

A traditional approach was chosen to verify process performance at commercial scale. Three consecutive PPQ batches were executed at commercial scale at the intended commercial manufacturing site.

Overall, the validation criteria are acceptable. A summary on the performed PPQ including the process and performance parameters per manufacturing step for each of the three PPQ batches, has been provided. Deviations were sufficiently described and evaluated/justified. All other process and performance parameters met their acceptance criteria or acceptance range. Continued process verification (CPV) will be undertaken to ensure the process is under a state of control.

Impurity clearance

Validation of clearance of process-related impurities and product-related impurities was performed by their measurement through the manufacturing process of PPQ batches. hcDNA has been demonstrated

to be cleared consistently. Residual host cell protein (rHCP) clearance has been demonstrated. The downstream process stagewise demonstrates the rProA clearance.

Product quality attributes of size and charge variants have been demonstrated to be within acceptable limits. Product-related impurities have been demonstrated to be consistently cleared to acceptable limits.

Hold times

Hold time data has been sufficiently validated. The proposed hold times are sufficiently justified.

Resin aging

The resin aging studies were conducted using scale down models. Qualification of a stepwise scale-down model (SDM) for the AVT06 active substance (AVT06-AS) downstream process to the full-scale process was performed and demonstrated.

The protocol for at-scale verification of chromatographic resin lifetime has been provided.

Active substance transport validation

The active substance transport validation studies were performed, and the results were found satisfactory.

Manufacturing process development

Over the course of development, AVT06-AS was processed at several scales; these manufacturing processes are termed as small-scale process, pilot process, and at-scale process. At-scale process was used for clinical batch manufacture and is the proposed commercial process used to supply for clinical studies, for process validation activities and planned commercial supply. Therefore, no comparability data is needed at AS level. This is acceptable.

Process characterisation

The manufacturing process for AVT06 40 mg/mL active substance was developed based on development studies and manufacturing experience.

The process risk assessment was evaluated by Failure mode and effects analysis (FMEA). CPPs that potentially impacted critical quality attributes were identified and selected for process characterisation (PC) studies. The list of evaluated parameters is considered comprehensive.

Proven Acceptable Ranges (PARs) were defined for CPPs based on performed process characterisation study using qualified SDMs. These SDMs were appropriately qualified and qualification reports were provided.

The characterisation study evaluated the impact of change in process parameters on active substance quality attributes. Both, the characterised range and established PAR were provided in dossier and PAR are used as limits for all CPPs and some nCPPs in the manufacturing control strategy as defined in 3.2.S.2.4. This approach is found acceptable.

The applicant performed comprehensive characterisation studies to evaluate the impact of the CPPs on CQAs within the characterised range of the process parameters and results of the design of experiments (DoE) studies and corresponding statistical analyses are available in the provided reports. The CPPs and non-CPPs were properly established based on the performed characterisation and the provided data support the proposed PARs.

Contact material compatibility

The compatibility of AVT06 formulated active substance (AVT06-AS) with the selected product contact materials was assessed. These contact materials are demonstrated to be compatible with AVT06-AS.

Furthermore, a risk assessment was carried out for all process stream contact materials within the AVT06 manufacturing process (AS and FP) along with their relevant process parameters and conditions that may affect the leaching profile of the material. The information provided is sufficient.

Characterisation

Elucidation of structure and other characteristics

The characterisation studies were conducted as part of the comparative analytical similarity assessment alongside the reference product, Eylea, and the results have been presented. The additional comparative characterisation studies are presented in section 3.2.R.3.6 Additional characterization for results and analysis.

The section 3.2.S.3.1-Elucidation of structure and other characteristics with physicochemical and functional characterisation data of AVT06-AS was provided with physicochemical and functional characterisation data of AVT06-AS. The information provided is considered sufficient.

Impurities

The impurity profile was analysed by testing product-related impurities/substances and process-related impurities. Furthermore, the applicant has assessed the risk of formation or introduction of nitrosamines in the manufacturing processes of AVT06 AS. The risk analysis demonstrates a low risk of the presence of nitrosamines in the AVT06-AS. This conclusion is supported based on the provided risk evaluation as no risk has been identified with regard to the risk factors related to nitrosamine formation as outlined in the Questions and answers on CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.

Product related impurities were identified and discussed. Their potential impact on safety/immunogenicity or functional activity was evaluated. The size and charged variants are controlled as part of release and shelf-life specification with appropriate acceptance criteria. Other product related impurities and variants related to higher order structure, post-translational modifications, hydrophobic variants were sufficiently evaluated as part of analytical similarity exercise, and they are consistently at the levels or below the levels observed in the reference product and/or the impact of these impurities on the safety/immunogenicity or functional activity is considered negligible. The overall control strategy for process and product related impurities is considered adequate.

2.2.2.3. Specification

The release and shelf-life specification for AVT06 AS includes general compendial tests (clarity, color, pH), compendial microbiological safety as well as in-house tests for identity, glycosylation, purity/impurity, potency, and content.

The acceptance criteria have been established by literature review, pharmacopoeia monographs, specified target product profile as well as evaluating analytical results from the available AVT06 batches representative of the final manufacturing process.

The proposed specification criteria are generally considered justified.

Analytical procedures

An overview of the analytical methods is included.

For the in-house methods sufficient details regarding principle of the method, equipment, reagents and materials, description of the procedure, data analysis and system suitability test and data reporting; for some of the methods representative chromatographs were also included.

For the validation of non-compendial methods, adequate summaries of validations or validation reports were provided. Most of the characteristics of the analytical procedures (e.g. accuracy, precision, specificity, linearity, range, quantitation limit) were validated as per ICH Q2 requirements.

Batch analysis

Information of active substance batches including manufacturing date and use of batch are provided. Batch analysis data from several representative commercial AVT06 active substance batches are provided.

All results comply with the specifications valid at time of testing and comply with the proposed commercial specifications (if applicable) as well.

In summary, the presented results demonstrate that the manufacturing process reliably delivers AS with consistent and acceptable quality.

Reference standard

A two-tiered approach as per ICH Q6B consisting of Primary Reference Material (PRS) and a Working or Secondary Reference Material (WRS/SRS) has been implemented in line with ICH Q6B. The primary reference material will be used to qualify the working reference material. The working reference material will be for routine use. This approach is endorsed.

A protocol to qualify the future working reference material has been provided and is acceptable.

The information provided in this section is deemed sufficient.

Container closure system

The primary container closure system used for AVT06 active substance (AVT06-AS) are sterile, pre-assembled, single-use containers (bag in shell) for freezing and thawing biopharmaceutical solutions. The bag in the shell container has been selected to ensure highest mechanical stress protection during container handling before and after storage.

A description of the container closure system has been provided, including a technical drawing and a table containing the identity of materials of construction of each primary packaging component. A representative certificate of conformance is included.

Suitability and protection of the container closure system has been confirmed by testing according to the relevant pharmacopeial monographs, stability, and integrity testing. Extractable testing was performed by using multiple solvents. Compounds identified in semi volatile and volatile analysis were briefly discussed. AVT06 40 mg/mL active substance stored in bags was subjected to leachable analysis. This analysis revealed that there is sufficient safety margin for each identified compound and that the identified leachables pose a negligible risk of an adverse patient safety effect. The overall conclusion is considered acceptable.

2.2.2.4. Stability

The AVT06-AS (active substance) stability program has been designed and conducted according to relevant guidance ICH Q5C and ICH Q1A.

All stability studies have been conducted using representative bags compared to the commercial primary packaging material for the active substance with the same interior product contact layer to those used to store the AVT06-AS.

All results comply with the shelf-life specifications. Based on the stability data provided, the proposed shelf-life for the active substance is considered acceptable.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

Description of the product

Mynzepli 40 mg/ml is presented as a sterile, preservative-free solution for intravitreal injection, containing 40 mg of aflibercept per 1 ml as active substance.

Other ingredients are: L-histidine, L-histidine monohydrochloride monohydrate, trehalose dehydrate, poloxamer 188, and water for injections.

The active substance is supplied at a target concentration 40 mg/mL in the final formulation, no additional dilution/formulation is performed during the manufacture of finished product.

The components of the finished product are appropriately described. All the excipients used in the FP comply with Ph. Eur. requirements. No excipients of human or animal origin are used.

The AVT06 finished product formulation differs from the Eylea formulation and contains buffer and stabilizing excipients (L-histidine, L-histidine monohydrochloride monohydrate, and trehalose dihydrate) at concentrations which are within the concentration range of other approved products for intravitreal administration.

The qualitative and quantitative composition of AVT06 FP along with the function and grade of excipients have been provided.

The product is available in:

- a vial (type I glass) with a stopper (elastomeric bromobutyl rubber), and an 18 G filter needle. Each 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.
- a pre-filled syringe (type I glass) marked with a dosing line, with a plunger stopper (elastomeric bromobutyl rubber) and a Luer lock adaptor with a tip cap (elastomeric rubber). Each pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept.-This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept.

Pharmaceutical development

The formulation development is well described. All excipients in the formulation are of compendial quality and have not been changed during development.

The quantity of poloxamer 188 in the formulation was selected following results of the formulation development studies. Neither non-clinical studies nor clinical studies have revealed any safety concerns as regards to the chosen concentration. The robustness of the formulation was tested. Sufficient information was provided.

Overages

There is no overage in AVT06-FP PFS and AVT06-FP vial formulation.

However, for AVT06-FP PFS an overfill is applied to deliver the intended dose of 0.05 mL. This overfill is required to ensure that every PFS meets the extractable volume requirements and can deliver the intended dose of 0.05 mL. The syringe barrel has a dosing line equivalent to 50 µL. The extractable volume is adequately justified.

For AVT06-FP vial an overfill to have an extractable volume of not less than 0.1 mL is applied. This overfill is required to ensure that every vial meets the extractable volume requirements and can deliver the intended dose of 0.05 mL. The extractable volume is adequately justified.

Manufacturing development

Modifications were made to the manufacturing process between the clinical lot manufacturing and the PPQ batches. These are considered as minor changes only served to improve process control and are considered low risk for impact to product quality attributes. The applicant presented several comparability studies.

Key in-process product quality attributes, release, and stability data, and extended characterisation data have been compared.

Overall, the studies showed that all AVT06-FP PFS batches manufactured from the scales and sites evaluated demonstrated comparable quality attributes. In relation to the comparability between AVT06-FP vial and AVT06- FP PFS, several batches were included in this study. According to the data submitted, no difference is highlighted between the two presentations.

Extended characterisation data and stability data, including accelerated and stressed stability, are presented for several AVT06-FP PFS batches. Overall, the study showed that all AVT06-FP PFS batches assessed demonstrated comparable product quality profile before and after surface sterilisation. It can be concluded that assembly, packaging, and surface sterilisation process do not have impact on the final quality and stability of finished product.

Container closure system (CCS)

PFS

The AVT06-FP PFS CCS consists of a single-use, pre-fillable 0.5 mL type I borosilicate glass syringe with a rubber stopper and Luer-lock cone that is assembled with integrated tip cap (ITC) and a pre-printed dosing line equivalent to 50 µL.

The CCS was selected to minimize the impact on the quality and stability of the finished product.

The safety of the CCS components for sterile products has been assessed by the syringe supplier, which includes a review of the sterilisation procedures and associated validations, as well as phthalates, allergens, elemental impurities, heavy metals, residual solvents, and nitrosamines. These were found to be in accordance with regulatory requirements.

Vial

The AVT06-FP Vial CCS consists of a single-use, 2R type I borosilicate glass vial (container), a rubber stopper (closure), and an aluminum flip-off crimp cap (seal).

The vial and the rubber stopper are Ph. Eur. compliant.

The suitability of the selected primary packaging material for its intended use is supported by stability study results, container closure integrity testing and extractables/leachables studies.

2.2.3.2. Manufacture of the product and process controls

Manufacturers - AVT06-FP PFS and AVT06-FP vial

Valid GMP certificates have been provided for all finished product manufacturing sites.

Description of manufacturing process and process controls

The AVT06-FP is manufactured by thawing, pooling, and mixing of the formulated AVT06-AS, followed by bioburden reduction filtration and transfer, sterile filtration, aseptic filling, stoppering, manual visual inspection, labelling and storage.

In-process controls have been sufficiently described.

The report of leachable analysis of in-process samples was submitted. No target compounds have been detected above the reporting threshold by target analysis.

The batch numbering system of AVT06-FP is sufficiently explained.

The applicant has clarified the batch numbering system following assembly and packaging and following surface sterilisation. Therefore, the traceability is confirmed throughout the manufacturing process.

Controls of critical steps and intermediates

The manufacturing process of AVT06-FP is controlled using IPCs, which are used for critical parameters containing acceptance criteria/action limits. Hold times are listed and correspond to values obtained from the batches tested during process validation.

There are no intermediates in the AVT06 finished product manufacturing process.

Process validation

Several consecutive PPQ batches were manufactured for the commercial presentations. All PPQ batches met the prospective acceptance criteria and in-process controls, and pre-defined specifications. The provided data demonstrates that when operating within the proposed ranges, the performance controls meet relevant quality criteria.

In line with the sterilisation guideline, the filter validation also included discussion on extractable and leachable substances from the filter. Extractables from the sterile filter were assessed and the results were provided. No target compounds have been detected above the reporting threshold by target analysis.

Media fill tests and filter validation studies have been successfully executed, and it is demonstrated that aseptic manufacturing is reliable and under control.

Overall, the process validation exercise is deemed acceptable.

Transport validation

Transport validation is performed to ensure that the quality of the finished product and integrity of the container closure system are maintained until it reaches the end-user.

2.2.3.3. Product specification

The release and shelf-life specification for AVT06 FP includes general compendial tests, compendial microbiological safety tests as well as in-house tests for identity, purity/impurity, potency, and content. Purity and impurity are determined by complementary methods.

The acceptance criteria have been established by literature review, pharmacopoeia monographs, relevant safety guidelines, specified target product profile as well as evaluating analytical results from the available at-scale batches. Additionally, introduction of new impurities (product-related or process-related) during finished product manufacture is not anticipated.

Evaluation of the risk of formation or introduction of nitrosamines in the finished product manufacturing processes has been completed and summarised. An acceptable risk assessment on nitrosamine impurities has been provided including AS manufacturing (sources materials and excipients), FP manufacturing, cross-contamination, reutilization, degradation process, and packaging.

The applicant´s conclusion that the risk for nitrosamine impurities is negligible can be agreed.

Elemental impurities were evaluated in line with ICH Q3D and there is no risk of elemental impurities from the manufacturing process.

Analytical procedures

An overview of the analytical methods is included. Appearance (colour and clarity), and pH as well as the safety relevant quality attributes endotoxin and microbial enumeration are tested according to the respective Ph. Eur. monographs. All other methods are in-house methods for which sufficient method descriptions have been provided.

The validation of analytical methods which are performed on both AS and FP has been presented in the AS. This is acceptable.

For the validation of non-compendial methods, adequate summaries of validations or validation reports were provided. Most of the characteristics of the analytical procedures (e.g. accuracy, precision, specificity, linearity, range, quantitation limit) were validated as per ICH Q2 requirements.

Batch analyses

For AVT06-FP PFS and AVT06-FP vial batch analyses are presented. All lots were released according to the specifications in place at the time of release. Overall, the results provided confirm consistency and uniformity of the product, indicating that the process is under control.

Reference standards or materials

The reference standards for FP are the same as those established for AS (see AS section).

Container closure system

PFS

The primary container closure system for AVT06 finished product PFS is a single-use, type I borosilicate glass pre-filled 0.5 mL syringe (container) with a luer-lock cone that is assembled with an integrated tip cap (ITC) (closure), a bromobutyl plunger stopper. The syringe barrel has a dosing line equivalent to 50 µL.

AVT06-FP PFS is an integral drug-device combination product within the meaning of Directive 2001/83/EC and applicable amendments, where the medicinal product provides the primary mode of action. the Notified body opinion has been submitted in accordance with the Medical Devices Regulation 2017/745, Article 117

Vial

The primary packaging for the AVT06-FP Vial consists of a clear colorless borosilicate type I glass vial closed with a rubber stopper. The rubber stopper is sealed with an aluminium crimping seal and a plastic flip-off cap component. The seal and the cap do not come into contact with AVT06-FP. The filter needle is CE marked and complies with applicable EU Directives/Regulation. The CE certificate is

provided. Sufficient information as regards the co-packaged filter needle has been included. The AVT06 DP-vial is packed into a cardboard box to protect the product from light.

Technical drawings and incoming specifications of all components of the primary packaging systems of AVT06 PFS and vial have been provided. The information provided is adequate and sufficient.

2.2.3.4. Stability of the product

A shelf-life of 24 months is proposed for the finished product when stored at the intended storage conditions at 2 °C to 8 °C.

Stability studies have been performed in line with relevant ICH guidelines with the proposed commercial process and CCS.

PFS

Three stability conditions have been studied: long-term storage conditions, accelerated storage conditions and stressed storage conditions.

Vial

Several commercial scale FP-vial batches were included in the stability study at long-term conditions, at accelerated conditions, and at stress conditions.

Based on the stability data provided the claimed shelf-life of 24 months for the PFS and vial finished product when stored at 2 °C to 8 °C is acceptable. The unopened blister may be stored outside the refrigerator below 25 °C for up to 24 hours.

A confirmatory photostability study for AVT06 FP was performed. AVT06-FP should be stored protected from light. Appropriate protection is ensured by the secondary packaging.

2.2.3.5. Biosimilarity

AVT06 is a proposed biosimilar to the reference medicinal product EU-Eylea and US-Eylea. Whereas pharmaceutical form and strength are identical, the formulations of AVT06 and the reference product differ.

To capture the representative range of the proposed biosimilar product, a comparability assessment of AVT06 2 mg/0.05 mL vial and AVT06 2 mg/0.05 mL PFS was conducted and the data from these two presentations are pooled together. Similarly, an analytical bridging assessment has been conducted to assess the comparability between EU-Eylea vial and EU- Eylea PFS, US-Eylea vial and US-Eylea PFS in order to pool the data from these two presentations to derive the quality ranges for analytical similarity assessment for each region.

The comparability exercise between AVT06-FP vial and AVT06-FP PFS is deemed acceptable. The applicant has also provided data to support the conclusion that EU- and US-Eylea can be considered analytically comparable.

The analytical similarity assessment is well presented in the dossier. Figures and tables summarising the individual results and data distribution for each parameter, chromatographs, spectra, electropherograms etc. have been included. The approach and methodology of the analytical similarity assessment is sufficiently described and overall acceptable.

AVT06-FP vial and PFS batches manufactured from independent commercial production scale and 1 pilot scale AVT06 active substance batches were included in the assessment. Additionally, the AVT06-FP vial batch used for pre-clinical study was included in the assessment.

The studies included multiple batches of EU-Eylea and ~~of~~ US-Eylea. Since some non-clinical studies (*in-vitro* studies) were conducted using CN (Chinese)-Eylea, several batches of CN-Eylea were also included in the study.

Several head-to-head comparative analytical similarity assessments were conducted during development and included analysis as part of QTPP assessments. Data from these head-to-head assessments were compiled to ensure a sufficient number of batches for analysis were available.

The total number of batches used for the cumulative comparative analytical similarity assessment was determined to allow understanding of the variability of AVT06 and reference product and to make a valid conclusion on similarity. Batches of AVT06 were assessed using the same primary product container closure system as used in the finished product presentations.

A QTPP was established using data from Eylea batches (vial and PFS). A risk ranking map matrix was established taking into account the impact of each attribute (effect on biological activity, pharmacokinetics/pharmacodynamics (PK/PD), immunogenicity, and safety) and the uncertainty). The risks were classified as very high, high, moderate and low. Some quality attributes were classified as obligatory CQA, due to their high criticality to product efficacy, safety, stability (in the case of strength and composition CQAs), or regulatory requirements.-

Analytical methods used in the similarity assessment

The selected comprehensive set of orthogonal state-of-the–art analytical methods which covers primary structure, higher order structure, N-glycosylation, charge variants, oxidation related variants, size variants, other variants, biological activity~~),~~ physical tests (particles and strength) appears adequate to address the relevant quality attributes of aflibercept

The VEGF receptor domain-mediated mechanism of action (MoA) was evaluated by an extensive range of biological assays that included binding to VEGF-A isoforms 165, 110, 121, and 189, and VEGF-B isoform B186, binding to PlGF-1, and -2, binding to Galectin-1, HUVEC anti-proliferation, VEGFR1-PlGF-1 binding inhibition, VEGF-A signaling inhibition (reporter gene) assay. Biological characteristics were further compared with regard to Fc receptor binding (FcγRIa, FcγRIIa 131H, FcγRIIb, FcγRIIIa 158V, FcγRIIIb, FcRn), C1q binding, absence of binding to VEGF-C and -D, and absence of CDC and ADCC activity. The descriptions and data for important method performance characteristics that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient and show suitability of the methods for the intended use.

Biosimilarity exercise

For many quality attributes and particularly for the MoA related activities, AVT06 was demonstrated to be analytically highly similar to EU-Eylea, US-Eylea and CN-Eylea. Results from several analytical methods show differences between AVT06 and EU-Eylea. These differences have been adequately evaluated by the applicant and are not expected to result in a different clinical performance of AVT06:

<u>Primary Structure</u>

The amino acid sequence of AVT06 is identical to EU-, US- and CN-Eylea and comparable peptide map profile was observed for these products. The sub-unit mass and de-N-glycosylated intact mass and sub-unit mass in AVT06 were similar to EU-, US- and CN-Eylea, barring intensity differences pertaining to the abundance of different glycan species in AVT06 and Eylea.

<u>Higher order structure</u>

The secondary structure, structural integrity, tertiary structure, disulfide linkages and trisulfide contents in AVT06 and EU-Eylea, US-Eylea and CN-Eylea were similar. The free thiol content in AVT06 batches were higher than the EU-Eylea US-Eylea () and CN-Eylea quality ranges. However, considering

the similarity demonstrated between AVT06 and Eylea in other physicochemical techniques and biological assays and in forced degradation and head-to-head stability studies, this difference in free thiol content is unlikely to impact the efficacy and safety of AVT06. The higher order structure related features were comparable between EU-, US- and CN-Eylea as well.

Post-translational modifications

Glycosylation

High mannose

The high mannose content in the AVT06 batches were higher than the quality ranges derived from EU-Eylea US-Eylea and CN-Eylea. The high-mannose group of glycans may influence PK via differential clearance through the mannose-binding receptors. However, only high mannose content at very high level is known to impact the clearance of therapeutic proteins and thus the slightly higher high mannose content observed in AVT06 batches is not expected to impact the clearance of the product. Additionally, high mannose glycans can also contribute to the afucosylated glycan content and impact FcγRIIIa and ADCC activity. However, the mechanism of action (MoA) of aflibercept does not involve ADCC effector function, and thus the difference observed in high mannose content between AVT06 and Eylea is not expected to have an impact. Nevertheless, high-mannose content in AVT06 is controlled to achieve a low level during active substance manufacturing through analytical control during batch release.

The justification as regards high mannose difference is acknowledged.

The high mannose levels in EU-Eylea, US-Eylea and CN-Eylea batches were comparable.

Galactosylation

The galactosylation levels in all the AVT06 batches are lower. Due to the absence of CDC and ADCC activities in the MoA of aflibercept, a difference in this attribute is not expected to have a meaningful impact. As expected, N-glycan species containing potentially immunogenic α 1,3-Gal residues were not detected in any of the AVT06 and Eylea batches analysed. Nevertheless, galactosylation content in AVT06 is controlled to achieve a high level (not less than acceptance criteria) during active substance manufacturing through analytical control during batch release.

The justification as regards galactosylation difference is acknowledged.

The galactosylation levels in EU-Eylea, US-Eylea and CN-Eylea batches were comparable.

Afucosylation

Total afucosylation levels in AVT06 was similar to the EU-, US- and CN-Eylea. The total afucosylation in EU-Eylea, US-Eylea and CN-Eylea batches were comparable.

Sialylation

The sialylation levels in AVT06 was similar to the EU-, US and CN-Eylea. The data from EU-Eylea and CN-Eylea were within the US-Eylea quality range, indicating comparability between the Eylea from these three regions as well.

Sialic acid

The total sialic acid content in AVT06 batches are within the quality range derived from the EU-Eylea batches. AVT06 batches show similar biological activity, compared to the rest of the AVT06 batches and Eylea batches and thus the small difference observed in total sialic acid content in these AVT06 batches is not expected to impact the safety and efficacy of AVT06. The level of NANA in AVT06 batches were comparable to the quality ranges derived from EU-Eylea, US-Eylea, and CN-Eylea. Very low levels of potentially immunogenic Neu5Gc residues were observed in both the products.

Site specific N-glycan analysis (N36, N68, N123, N196 and N282)

Overall, the predominant species are similar in AVT06 and EU-, US- and CN-Eylea batches at each N-Glycan site and the results reported here are consistent with the total N-glycan analysis. The galactosylation content was lower in AVT06 at all the five sites, leading to the considerably lower total galactosylation content, while the high mannose content in N123 and N196 led to the lower high mannose content in AVT06. As discussed in the overall glycan section, these differences are not meaningful.

The site-specific N-glycan distribution in EU-, US- and CN-Eylea was comparable.

Several AVT06 batches showed slightly higher MP1 variant than EU-Eylea quality range indicating relatively lower N68 glycan occupancy in AVT06. The role of N68 glycosylation in VEGFR1 functionality is not very clear. However, from the available structural information, it is evident that the N68 glycan is facing away from the binding site and thus may not be directly relevant for VEGFR1 functionality. Accordingly, as shown in the functional activity section, the in vitro potency and target binding activity of AVT06 is similar to EU- and US-Eylea, indicating the small difference observed in N68 glycan occupancy does not impact the efficacy of AVT06.

O-glycosylation

It is confirmed that O-glycosylation as absent in AVT06 batches.

Oxidation

The relative oxidation at all the methionine sites in AVT06 was similar to or lower than the quality ranges derived from the EU-, US- and CN-Eylea.

The oxidation levels in all these methionine sites were comparable between EU-, US- and CN-Eylea.

Deamidation

The deamidation levels were lower in AVT06 batches at all the four sites, compared to EU-, US- and CN-Eylea batches. The deamidation is a quality attribute with low criticality and thus the lower deamidation in AVT06 is not expected to impact the efficacy and/or safety of the product.

The deamidation levels at all the sites was comparable between EU-, US- and CN-Eylea batches.

Aspartate isomerization

Trace amounts of iso-Asp were detected at three aspartic acid sites in AVT06 and Eylea batches, and the relative abundance of iso-asp formation at all the sites in AVT06 were similar to the quality range derived from the EU-, US- and CN-Eylea batches analysed.

Iso-Asp formation

HPLC based assay using IsoQuant kit was used to assess the levels of iso-aspartic acid in AVT06 and Eylea batches. This method detects iso-aspartic acid derived from both asparagine and aspartic acid, however, based on the low levels of isomerization of aspartic acid detected, most of the iso-aspartic acid is formed through deamidation in AVT06 and Eylea. Subsequently, the iso-asp content in AVT06 batches was lower than the EU-, US- and CN-Eylea quality ranges.

The iso-asp levels in EU-, US- and CN-Eylea were comparable.

N-/C- terminal integrity

The C-terminal lysine content in AVT06 batches was higher than the EU-, US- and CN-Eylea, while the proline amidation content was significantly lower. The C-terminal lysine is not known to impact the safety and/or efficacy of the product, and thus, this slight difference can be considered not meaningful.

Similar levels of N-terminal signalling sequence remnant and fragmentation were detected in AVT06 and Eylea batches.

The C- and N-terminal variants were comparable between EU-, US- and CN-Eylea batches.

Functional activity

VEGFR related assays

Cell-based potency assay (HEK-KDR): the potency of AVT06 was similar to EU- and US-Eylea, indicating similar functional activity in AVT06 and Eylea. Comparable potency was determined in EU-Eylea and US-Eylea, and the potency of the CN-Eylea batches lie within the quality ranges derived from EU- and US-Eylea.

Inhibition of proliferation of HUVEC cell: the AVT06 potency determined by inhibition of HUVEC cells assay was similar to the EU- and US-Eylea.

VEGFR1-PlGF-1 binding inhibition assay: the cell-based potency of AVT06 was similar to Eylea and fell within the range of EU and US Eylea and values of AVT06 fluctuate only slightly with CN Eylea batches.

$VEGFA_{165}$ binding: the VEGFA165 binding of AVT06 was similar to Eylea and was within the quality range) of EU-, US- and CN-Eylea. The VEGFA165 binding ability of EU-, US- and CN-Eylea was comparable as well.

$VEGFA_{121}$ binding: The $VEGFA_{121}$ binding of all the AVT06 batches were similar to the US- and CN-Eylea batches. On the other hand, AVT06, except for one all other batches showed similar $VEGFA_{121}$ binding, compared to the EU-Eylea quality range. A few minor outliers are not considered meaningful and attributed to method variability.

The $VEGFA_{121}$ binding ability of EU-, US- and CN-Eylea was comparable as well.

$VEGFA_{189}$ binding: $VEGFA_{189}$ binding of AVT06 was similar to EU-, US- and CN-Eylea and the binding ability was comparable within the Eylea batches from these three regions as well.

$VEGFA_{110}$ binding: the $VEGFA_{110}$ binding of all the AVT06 batches was similar to the US- and CN-Eylea batches. On the other hand, Similar $VEGFA_{110}$ binding for few AVT06 batches was within the EU-Eylea quality range, while the data from the remaining AVT06 batches were slightly higher or lower than the quality range derived from EU-Eylea batches. The observed differences in $VEGFA_{110}$ binding is attributed to method variability of the SPR based assays and is considered non-relevant.

$VEGFB_{186}$ binding: the VEGFB binding of AVT06 was similar to EU-Eylea and CN-Eylea

The $VEGFB_{186}$ binding ability of EU-, US- and CN-Eylea was comparable as well.

PlGF-1 binding and PlGF-2 binding: PlGF-1 binding PlGF-2 binding of AVT06 was similar to EU-, US- and CN-Eylea and the binding ability was comparable within the Eylea batches from these three regions as well.

Galectin-1 binding: The Galectin-1 binding of AVT06 batches were within the quality ranges derived from EU- and US-Eylea batches, while batches were within the CN-Eylea quality range (results for the other batches were slightly higher than the quality ranges). However, considering that the role of Galectin-1 binding in aflibercept MoA is not thoroughly established, and the similarity of AVT06 with Eylea, in terms of relative potency and $VEGFA_{165}$, VEGFB, PlGF-1 and PlGF-2 binding has been established, the differences in Galectin-1 binding is not expected to impact the safety and efficacy of AVT06.

VEGFC and VEGFD binding: The results demonstrated that AVT06 as well as Eylea were unable to bind VEGFC or VEGFD.

Fc related activities:

FcRn binding of AVT06 was similar to EU-, US- and CN-Eylea and the binding ability was comparable within the Eylea batches from these three regions as well.

FcγRIa binding of AVT06 was similar to EU-, US- and CN-Eylea.

The FcγRIIa 131H binding of AVT06 batches was lower than the EU-, US- and CN-Eylea batches tested, however, they were within the quality ranges derived from EU-Eylea and CN-Eylea. MoA of aflibercept does not involve effector function, thus the lower FcγRIIa 131H binding of AVT06 is unlikely to impact the efficacy and safety of the product.

The FcγRIIb binding of AVT06 batches was lower than the EU-, US- and CN-Eylea batches tested. MoA of aflibercept does not involve effector function, thus the lower FcγRIIb binding of AVT06 is unlikely to impact the efficacy and safety of the product.

The FcγRIIIa binding of AVT06 was lower than the quality ranges derived from EU-, US- and CN-Eylea. The lower FcγRIIIa binding in AVT06 may be attributed to the lower galactosylation in AVT06. MoA of aflibercept does not involve effector function and neither AVT06 nor Eylea show any ADCC activity, and thus the lower FcγRIIIa binding of AVT06 is unlikely to impact the efficacy and safety of the product.

The FcγRIIIb binding of AVT06 is lower than the quality ranges derived from the EU- and US- Eylea. MoA of aflibercept does not involve effector function, thus the lower FcγRIIIb binding of AVT06 is unlikely to impact the efficacy and safety of the product.

For the tested Fcγ-related functions, the binding has been shown to be comparable. The applicant has provided the binding constants, confirmed the similarity of the binding curves and provided a description of the assays, including positive and negative controls.

C1q binding of AVT06 was similar to EU-, US- and CN-Eylea.

Physicochemical analyses

Protein content

The protein content in all of AVT06 batches measured except one were within the quality range derived from EU, US- and CN-Eylea batches, while one AVT06 batch was slightly higher. Considering no consistent increase during storage was observed during the stability study of any of the AVT06 batches, this slightly higher protein concentration recorded for this one AVT06 batch during the analytical similarity study can be considered as method variability and thus not relevant in terms of safety and efficacy of AVT06.

Charge heterogeneity

The charge variant profiles of AVT06 and EU-, US- and CN-Eylea were similar, and the relative abundance of R1, R2 and R3 regions were also similar in AVT06 and EU-Eylea, US-Eylea and CN-Eylea. The AVT06 batches had very low amounts of late-R3 peaks, while these were not detected in the originator products. Generally, charge variants present in these low amounts should not impact the efficacy and safety of the product. Nonetheless, a detailed characterisation of these peaks was conducted using late-R3 enriched fractions from downstream CEX purification process step. These peaks are found to have slightly lower levels of sialylation compared to the rest of the peaks and the glycan occupancy at N68 site was also lower in the late-R3 enriched fractions. However, no new species were observed in late-R3 enriched fractions, and the functional activity of these fractions are similar in AVT06 and Eylea. Absence of these very low abundance peaks in Eylea may relate to the considerably higher deamidation in Eylea, resulting in acidic shift of the far basic peaks.

The abundance of acidic peaks by cIEF post sialidase treatment was lower in AVT06, compared to the EU-, US- and CN-Eylea. The lower deamidation content in AVT06 is not expected to impact the safety and efficacy of the product.

The abundance of basic peaks was higher in AVT06, most likely due to the higher levels of C-terminal lysine content in AVT06.

Hydrophobic variants (HIC)

Aflibercept contains five potential glycosylation sites in both the chains and one of these sites is partially glycosylated. Thus, aflibercept can potentially have three main hydrophobic variants; 1. all the five sites in both the chains are glycosylated, 2. all the five sites in one chain are glycosylated, while only four sites in the other chain are glycosylated, and 3. only four sites in both the chains are glycosylated. These three variants are depicted as peak 1, peak 2 and peak 3, respectively in the HIC profiles.

The abundance of peak 1 is slightly lower in AVT06 batches, compared to the EU-, US- and CN-Eylea batches, while the contribution from peak 2 and peak 3 are slightly higher, indicating slightly lower glycan occupancy at N68 site in AVT06. As shown in section 9.3.1.3, the abundance of unoccupied N68 in AVT06 batches, was on the higher side of the quality ranges derived from the EU-, US- and CN-Eylea batches. The role of N68 glycosylation in VEGFR1 functionality is not very clear. However, from the available structural information, it is evident that the N68 glycan is facing away from the binding site and thus may not be directly relevant for VEGFR1 functionality. Accordingly, as shown in the functional activity section, the in vitro potency and target binding activity of AVT06 is similar to EU- and US-Eylea, indicating the small difference observed in N68 glycan occupancy does not impact the efficacy of AVT06. Additionally, the differences in deamidation content between AVT06 and Eylea can also contribute to the differences observed in HIC, and as mentioned in section 9.3.3, the lower deamidation content in AVT06 is not expected to impact the safety and efficacy of the product.

Size variants

The HMW levels in AVT06 batches by SEC-HPLC were lower than the EU-, US- and CN-Eylea batches and subsequently main peak contributions were higher. The HMWs and main peak distribution in EU-, US- and CN-Eylea was comparable.

The dimer and higher order aggregate content by SV-AUC was lower in AVT06, compared to the EU-, US- and CN-Eylea batches, in both the detection conditions, indicating lower proteinaceous and non-proteinaceous higher molecular weight species in AVT06.

The molar mass of the main peak and the HMWs in AVT06 and EU- and US-Eylea by SEC-MALS are similar.

The total fragments content by CE-SDS reduced was lower in AVT06 batches compared to EU-, US- and CN-Eylea batches. The abundance of MP1 and MP2 in some of the AVT06 batches were higher compared to the quality ranges derived from the EU-and US-Eylea batches, while the MP2 was lower than the EU- and US-Eylea quality ranges for some batches. Overall, this could be due to a combined effect of higher main peak (MP1+MP2) content (due to lower fragmentation in AVT06) and slightly lower N68 glycan occupancy in AVT06 batches. As discussed in the HIC section, the marginal differences in N68 glycan occupancy are not expected to impact the safety and efficacy of AVT06.

The non-reduced CE-SDS profiles of AVT06 and Eylea were similar and low molecular weight impurity content was lower in AVT06 compared to EU-, US- and CN-Eylea.

Sub-visible particles

The Z-averages of all the AVT06 batches by DLS are within the ranges of the EU-, US- and CN-Eylea. The polydispersity of most of the AVT06 batches are within the EU-, US- and CN-Eylea ranges, while some of the batches are slightly higher. Overall, the sub-visible particles measured by DLS in AVT06 were similar to the EU-, US- and CN-Eylea.

The number of particles observed in AVT06 are higher in AVT06, compared to EU- and US-Eylea, however, considering the method variability, the number of particles reported for AVT06 and Eylea are of same order of magnitude and thus are qualitatively similar.

Additional characterisation studies

To further strengthen the similarity claim, a head-to-head stability assessment was performed at long-term conditions, accelerated and stressed conditions between AVT06-FP vial, EU-Eylea vial and EU-Eylea PFS. Similar stability trends are observed for AVT06-FP Vial and EU-Eylea for all parameters evaluated at all storage conditions.

Conclusion

In summary, the presented analytical data demonstrate analytical similarity of the proposed biosimilar AVT06-FP and the reference product EU-Eylea. Minor analytical differences have been appropriately assessed by the applicant regarding their potential impact on clinical performance of the product. The observed differences are not expected to adversely impact clinical performance of AVT06-FP. The applicant has provided data in an attached report and a summary in section 3.2.R.3.4 to support the conclusion that EU- and US-Eylea can be considered analytically comparable. No data were provided as regards the bridging of CN-Eylea vs. EU-Eylea. No US-Eylea or CN-Eylea was used in clinical studies, only EU-Eylea.

From the quality perspective AVT06-FP is considered similar to EU-Eylea and is considered approvable as proposed biosimilar to Eylea.

Table 1: Summary of AVT06 analytical similarity with EU-Eylea

Attribute		**Method**	**Similarity conclusion**
Primary structure		Amino acid sequence	Identical amino acid sequence for AVT06 and EU-Eylea, including the N-terminal signalling sequence remnant.
		Native and de-N-glycosylated sub-unit mass (LC-MS) and de-N-glycosylated intact mass	Similar molecular mass and size demonstrated at the deglycosylated intact and sub-unit level for AVT06 and EU-Eylea.
Higher order structure	Secondary	Far-UV CD	Similar Far-UV CD profiles for AVT06 and EU-Eylea.
		FT-IR	Similar FT-IR profiles for AVT06 and EU-Eylea.
		DSC	Similar DSC profiles and melting temperatures for AVT06 and EU-Eylea.
	Tertiary, including disulfide and trisulfide bonds	Near-UV CD	Similar tertiary structure and identical disulfide bond connectivity demonstrated for AVT06 and EU-Eylea. Very low amounts of trisulfides detected in AVT06 and Eylea batches.
		Non-reduced peptide mapping (LC-MS)	
	Free thiols	Ellman´s reagent	Slightly higher free thiol content in AVT06, compared to EU-Eylea batches. However as demonstrated by the other techniques in this

Attribute		Method	Similarity conclusion
			study, this marginal difference in free thiol content does not impact the structural and biological attributes of AVT06. Further, the degradation profile of AVT06 was demonstrated as similar to EU-Eylea by forced degradation and H2H stability studies reconfirming the integrity of the structural features of AVT06
Post-translational modifications	Glycosylation	Rapifluor	Similar glycan distribution profile, structure, and composition for AVT06 and EU-Eylea.
	High mannose		High mannose levels for AVT06 are higher than that of the EU-Eylea. The high-mannose group of glycans may influence PK via differential clearance through the mannose-binding receptors [1]. However, only high mannose content at very high level is known to impact the clearance of the therapeutic proteins [1] and thus the slightly higher high mannose content observed in AVT06 batches are not expected to impact the clearance of the product. Additionally, high-mannose levels at Fc correlate with significant binding to FcγRIIIa and ADCC activity. However, the (MoA) of aflibercept does not involve ADCC effector function, and thus the difference observed in high mannose content between AVT06 and Eylea is not expected to have an impact. Nevertheless, high-mannose content in AVT06 is controlled to a low level during drug substance manufacturing through analytical control during batch release.
	Afucosylation		Total afucosylation levels in AVT06 were similar to EU-Eylea, while the levels of afucosylation without high mannose were slightly lower. Due to the absence of ADCC and FcγRIIIa involvement in the MoA of aflibercept, a difference in this attribute is not expected to have a meaningful impact.
	Terminal galactose		Lower terminal galactosylation levels in AVT06 compared to EU-Eylea. The levels of Fc galactosylation can impact complement protein (C1q) binding and in-vitro CDC activity of IgG1 antibodies. However, the MoA of aflibercept does not involve any effector function, and there is no documented evidence on involvement of VEGF-receptor galactosylation in VEGF binding. Thus, this difference in

Attribute		Method	Similarity conclusion
			galactosylation is unlikely to impact the efficacy of AVT06. The lack of impact of this difference in AVT06 functional activities are also demonstrated by the potency and binding assays in this study.
	Sialylation		Similar levels of sialylation for AVT06 and EU-Eylea were found.
	Glycan occupancy at N68	Reduced CE-SDS	Few AVT06 batches showed slightly higher MP1 variant than EU-Eylea quality range indicating relatively lower N68 glycan occupancy in AVT06. The role of N68 glycosylation in VEGFR1 functionality is not very clear. However, from the available structural information, it is evident that the N68 glycan is facing away from the binding site and thus may not be directly relevant for VEGFR1 functionality. Accordingly, as shown in the functional activity section, the in vitro potency and target binding activity of AVT06 is similar to the EU-Eylea batches, indicating the small difference observed in N68 glycan occupancy does not impact the efficacy of AVT06.
	Sialic acid content (mol/mol)	HPLC with DMB labelling	Similar levels of total sialic acid content for AVT06 and EU-Eylea, Neu5Ac being the predominant sialic acid. Very low levels of potentially immunogenic Neu5Gc residues were observed in both products. Additionally, very low levels of O-acetyl sialic acid species were observed in AVT06 and EU-Eylea batches and the abundance of these species was higher in AVT06 compared to EU-Eylea. O-acetyl sialic acid species are not known to impart any additional immunogenic response and are not expected to have an impact on the safety and efficacy of the product. This is supported by the target binding and potency data
	Iso-asp formation	HPLC	Lower levels of iso-asp in AVT06, compared to EU-Eylea. Iso-asp is predominantly formed through deamidation. Deamidation is a very low critical quality attribute and thus the lower deamidation in AVT06 is not expected to impact the efficacy and/or safety of the product.
	Deamidation	Peptide mapping (LC-MS)	Lower levels of deamidation in AVT06, compared to EU-Eylea. The deamidation is a very low critical quality attribute and thus the lower deamidation in AVT06 is not expected to impact the efficacy and/or safety of the product.

Attribute		Method	Similarity conclusion
	Met Oxidation		Similar or lower levels of Met oxidation detected in AVT06, compared to EU-Eylea.
	Trp Oxidation		Similar or lower levels of Trp oxidation detected in AVT06, compared to EU-Eylea.
	Aspartate isomerization		Very low and similar levels of aspartate isomerization for AVT06 and EU-Eylea.
	N/C-terminal integrity		Similar levels of N-terminal signaling sequence remnant and fragmentation were detected in AVT06 and EU-Eylea. Lower levels of proline amidation in AVT06, compared to EU-Eylea. Higher levels of C-terminal lysine detected in AVT06, compared to EU-Eylea. Both proline amidation and C-terminal lysine variants are considered as very low critical quality attributes and thus these differences are not expected to impact the safety and efficacy of AVT06.
VEGFR related activities	Potency	Cell-based potency assay (HEK-KDR)	Similar potency for AVT06 and EU-Eylea.
		Inhibition of proliferation of HUVEC cells	Similar potency for AVT06 and EU-Eylea
	VEGFA165 binding	VEGFA binding SPR	Similar VEGFA165 binding for AVT06 and EU-Eylea.
	VEGFA121 binding	VEGFA binding SPR	Similar VEGFA121 binding for several AVT06 batches tested and EU-Eylea. A batch showed slightly higher binding affinity compared to the EU-Eylea quality range. However, the AVT06 batch show comparable physicochemical properties compared to the other AVT06 batches, comparable VEGFA165, VEGFB and PIGF1 binding and comparable potency compared to the Eylea quality range, and thus the slightly different VEGFA121 binding is not considered meaningful and attributed to method variability.
	VEGFA189 binding	VEGFA binding SPR	Similar VEGFA189 binding for AVT06 and EU-Eylea.
	VEGFA110 binding	VEGFA binding SPR	Similar VEGFA110 binding for few AVT06 batches tested and EU-Eylea, while the data from other few AVT06 batches were slightly higher or lower than the quality range derived from EU-Eylea batches. The quality range derived from EU-Eylea batches was very narrow as few EU-Eylea batches were tested for this attribute. Considering the rest of the physicochemical and biological attributes of these few AVT06

Attribute		Method	Similarity conclusion
			batches were comparable to the other AVT06 batches and the expected method variability of the SPR based assays, the difference in relative binding observed in VEGFA110 binding is considered non-relevant.
	VEGFB186 binding	VEGFB binding SPR	Similar VEGFB186 binding for AVT06 and EU-Eylea.
	PlGF-1 binding	PlGF binding SPR	Similar PIGF-1 binding for AVT06 and EU-Eylea.
	PlGF-2 binding	PlGF binding SPR	Similar PIGF-2 binding for AVT06 and EU-Eylea.
	VEGFC and VEGFD binding	SPR	few AVT06, EU-Eylea and US-Eylea batches were tested for VEGFC and VEGFD binding by SPR method. VEGFA binding to AVT06 was used as positive control to demonstrate the activity of aflibercept in this assay, and VEGFR2 and VEGFR3 were used as positive controls for VEGFC and VEGFD binding, respectively. While significant binding of AVT06 with VEGFA, VEGFR2 to VEGFC and VEGFR3 to VEGFD were detected, any binding of aflibercept (AVT06 and Eylea) to VEGFC or VEGFD were not detected.
Characterization of Fc	FcRn binding	FcRn binding SPR	Similar FcRn binding for AVT06 and EU-Eylea.
	FcγRIa binding	FcγRIa binding SPR	Similar FcγRIa binding for AVT06 and EU-Eylea.
	FcγRIIa binding	FcγRIIa binding SPR	Similar FcγRIIa binding for AVT06 and EU-Eylea.
	FcγRIIb binding	FcγRIIb binding SPR	Sligtly lower FcγRIIb binding in AVT06, compared to the EU-Eylea. Since the mechanism of action of aflibercpet does not involve Fc mediated receptor functions, this difference is not expected to have any impact in efficacy and safety of AVT06.
	FcγRIIIa binding	FcγRIIIa binding SPR	The FcγRIIIa binding of AVT06 is lower than the quality range derived from the EU-Eylea. As demonstrated by lack of ADCC and CDC activity in AVT06 and EU-Eylea, the mechanism of action of aflibercept does not involve effector function, thus the lower FcγRIIIa binding of AVT06 is unlikely to impact the efficacy and safety of the product.
	FcγRIIIb binding	FcγRIIIb binding SPR	The FcγRIIIb binding of AVT06 is lower than the quality range derived from the EU-Eylea. As demonstrated by lack of ADCC and CDC activity in AVT06 and EU-Eylea, the mechanism of action of aflibercept does not involve effector function, thus the lower FcγRIIIb binding of AVT06 is unlikely to impact the efficacy and safety of the product.

Attribute		Method	Similarity conclusion
	C1q binding	SPR	Similar C1q binding for AVT06 and EU-Eylea.
	ADCC	Reporter assay	ADCC and CDC activity of few AVT06, EU-Eylea and US-Eylea batches were tested by reporter assay. SK-UT-1B cell line was used as target cells and the CHOmTNFα + adalimumab+ effector cells/human serum condition was used as the positive control showing induction of ADCC/CDC given the combination of a membrane-bound target and an effector function- inducing antibody. For both the assays, the control samples were able to induce the effector functions in all the plates, while all the AVT06 and Eylea samples failed to induce ADCC or CDC activities.
	CDC	Reporter assay	
Product related variants and impurities	Charge variants	cIEF	Similar charge profile and contents in AVT06 and EU-Eylea.
		cIEF + sialidase	Lower acidic variant and higher basic variant content in AVT06, compared to EU-Eylea, reflecting the lower deamidation and higher C-terminal lysine variants in AVT06. Both these attributes are low critical quality attributes and thus are not expected to induce any safety or efficacy related impact.
	Hydrophobic variants	HIC	The abundance of the most hydrophobic peak is slightly lower in AVT06 batches, compared to the EU-Eylea batches, while the contributions from the hydrophilic peaks are slightly higher, indicating slightly lower glycan occupancy at N68 site in AVT06. However, these differences are not expected to impact the efficacy of AVT06 due to the reasons outlined in N-glycan occupancy section.
	Size variants	CE-SDS reduced and non-reduced	Lower levels of fragmentation in AVT06, compared to the EU-Eylea, as depicted by reduced and non-reduced CE-SDS. Few AVT06 batches showed slightly higher MP1 variant than EU-Eylea quality range indicating relatively lower N68 glycan occupancy in AVT06. However, these differences are not expected to impact the efficacy of AVT06 due to the reasons outlined in N-glycan occupancy section.
		SEC-HPLC	Lower levels of HMW in AVT06, compared to EU-Eylea.
		SV-AUC	Lower levels of HMW in AVT06, compared to EU-Eylea.
	Protein content	OD280	The protein content in several AVT06 batches is within the quality range derived from EU-Eylea batches. The concentration recorded

Attribute		Method	Similarity conclusion
			was very close to the target concentration (40 mg/mL) and was well within the release and stability acceptance criteria Moreover, the concentration of this batch was recorded during release. Thus, considering any consistent increase in stability was not observed during the stability study of any of the AVT06 batches, this slightly higher protein concentration recorded during the analytical similarity study can be considered as method variability and thus not relevant in terms of safety and efficacy of AVT06.
	Sub-visible particle	DLS	Similar size and distribution of sub-visible particles in AVT06 and EU-Eylea.

2.2.3.6. Adventitious agents

No materials of animal origin are used in establishing of MCB/WCB and in the manufacture of AS/FP and the materials that conforms to the requirements as defined in the Guideline EMEA/410/01 "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" were provided in the dossier. Animal components are limited to tallow derivatives used in manufacture of polymeric resin for single use materials. Statements of compliance to EMA/410/01 were provided in dossier for all relevant materials.

All raw materials are tested according to the provided CoA.

The provided information is considered acceptable, no risk with regard to materials of biological origin has been identified.

Viral adventitious agents

The MCB and the PPCB were tested for the presence of adventitious agents in compliance with the ICH Q5A guideline. The unprocessed bulk was tested for the presence of adventitious agents on several batches in accordance with ICH Q5A guideline. The information provided is adequate and sufficient.

The viral clearance studies were performed with the potential worst-case conditions on scale down model (SDM) representative of full-scale manufacturing process.

The information provided is sufficient and acceptable and demonstrate that adventitious agents safety including TSE have been sufficiently assured.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Mynzepli has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Eylea.

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner.

The FP is manufactured according to a standard process. The manufacturing process is appropriately described, and process parameters are sufficiently justified based on process characterisation and validation data. The validation of the manufacturing process has been satisfactorily demonstrated

ensuring the manufacturing process for Mynzepli is capable of consistent and robust performance. Adventitious agents safety including TSE have been sufficiently assured.

Two Major Objections (MOs) were raised during the evaluation. MO1 concerning the missing documentation on compliance of the medical device with the requirements of Annex I MDR 2017/745 and MO2 regarding the finished product stability, were adequately addressed by the applicant.

Biosimilarity versus the reference product was sufficiently demonstrated. The panel of methods performed is satisfactory covering structural as well as biologicals quality attributes with the necessary level of depth. From the quality perspective, Mynzepli is considered similar to EU-Eylea and is approvable as proposed biosimilar to Eylea. No quality aspects impacting on the Benefit-Risk balance have been identified.

Overall, the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Mynzepli is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. Biosimilarity versus the reference product was sufficiently demonstrated.

In conclusion, based on the review of the data provided, the marketing authorisation application for Mynzepli is considered approvable as proposed biosimilar to Eylea from the quality point of view.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Mynzepli is developed as a proposed biosimilar of aflibercept (Eylea, reference medicinal product (RMP)) for the same use with respect of administration (intravitreal injection (IVT) only), and therapeutic indications approved for Eylea 40 mg/mL solution for injection in a vial.

Aflibercept is synthesized by Chinese hamster ovary (CHO) K1 cells as a dimeric, secreted and soluble protein. It 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 Mynzepli and Eylea have been shown to be identical.

Aflibercept acts as a soluble decoy receptor that binds to multiple isoforms of human VEGF-A, VEGF-B and PlGF, preventing it from interacting with its receptors (VEGFR-1 and VEGFR-2).

The Mynzepli finished product formulation differs from the Eylea formulation, especially regarding the use of poloxamer 188 that it is not used in approved products with IVT route of administration.

Although poloxamer 188 has been used as a surfactant in approved ocular product for subretinal injection, Luxturna®.

The non-clinical development relies on in vitro similarity studies to evaluate biological properties of Mynzepli and to demonstrate its biosimilarity to EU-, US- and CN-Eylea. Although in vivo studies are 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), several in vivo studies were conducted by the applicant in order to assess the safety of use of poloxamer 188 and to underline similarity of Mynzepli FP with Eylea.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

A number of in vitro pharmacology assessments to compare biological properties (VEGF- or Fc-related) of AVT06 and Eylea as part of quality evaluation. Comparability was performed with EU-, US- and CN-Eylea batches.

The details of the analysis performed, and the similarity outcome are summarised below:

Purpose	Results	Similarity outcome
VEGFR related activities		
Cell-based potency assay (HEK-KDR)	• Mynzepli ≈ EU- and US-Eylea batches • Few of Mynzepli batches > CN- Eylea batches (but quality range within quality range EU and Us-Eylea batches)	acceptable
Inhibition of proliferation of HUVEC cells	• Mynzepli ≈ EU- and Us-Eylea batches • CN-batches not tested	yes
VEGFA165 binding	• VEGFA165 binding: Mynzepli ≈ EU, US- and CN-Eylea batches	**yes**
VEGFA121 binding	• $VEGFA_{121}$ binding: Mynzepli ≈ US- and CN-Eylea batches • A Mynzepli vial batch with higher affinity than EU-Eylea batches → not expected to have relevant impact	**yes**
VEGFA189 binding	• VEGFA189 binding: Mynzepli ≈ EU-, US- and CN-Eylea batches	**yes**
VEGFA110 binding	• VEGFA110 binding: Mynzepli ≈ US- and CN-Eylea batches • Slight difference between Mynzepli and EU-Eylea batches → not expected to have relevant impact	**acceptable**
VEGFB186 binding	• VEGFB186 binding: Mynzepli ≈ EU-Eylea and CN-Eylea batches • Few Mynzepli vials batches binding slightly higher than for US-Eylea batches → not expected to have relevant impact	**acceptable**
PlGF-1 binding	• PlGF-1 binding: Mynzepli ≈ Eylea EU-, US- and CN-batches	**yes**

PlGF-2 binding	• PlGF-2 binding: Mynzepli ≈ Eylea EU-, US- and CN-batches	**yes**
Galectin-1 binding	• Galectin-1 binding: Mynzepli ≥ Eylea batches • role of Galectin-1 binding in aflibercept MoA is not thoroughly established but not expected to have an impact on safety or efficacy	**acceptable**
VGEFC and VEGFD binding	• Mynzepli baches vs US- and EU-Eylea batches → no binding for both	**yes**
Characterization of Fc		
FcRn binding	• FcRn binding: Mynzepli ≈ EU-, US- and CN-Eylea	**yes**
FcγRIa binding	• FcγRIa binding: Mynzepli ≈ EU-, US- and CN-Eylea	**yes**
FcγRIIa binding	• Mynzepli batches < EU- , US- and CN-Eylea batches • MoA of aflibercept does not involve effector function → lower FcγRIIa binding of Mynzepli unlikely to impact efficacy and safety	acceptable
FcγRIIb binding	• Mynzepli batches < EU- , US- and CN-Eylea batches • MoA of aflibercept does not involve effector function → lower FcγRIIb binding of Mynzepli unlikely to impact efficacy and safety	acceptable
FcγRIIIa binding	• Mynzepli batches < EU- , US- and CN-Eylea batches • MoA of aflibercept does not involve effector function and no ADCC activity triggered by Eylea → lower Fcι RIIIa binding of Mynzepli unlikely to impact efficacy and safety	acceptable
FcγRIIIb binding	• Mynzepli batches < EU- , US- and CN-Eylea batches • MoA of aflibercept does not involve effector function → lower Fcι RIIIb binding of Mynzepli unlikely to impact efficacy and safety	acceptable
C1q binding	• Mynzepli ≈ EU- , US- and CN-Eylea batches	yes

In general, Mynzepli appears to exhibit similar VEGF-related and Fc-related biological activities as the RMP although some differences were noted not considered meaningful by the applicant (see Quality AR).

From a non-clinical point of view the outcome of the investigation is the following.

Regarding VEGFR activities, differences were observed in the Cell-based potency assay (HEK-KDR) wherein potency of Mynzepli batches was in average higher that CN- Eylea batches (but quality range within quality range EU and Us-Eylea batches). Also a slight difference between Mynzepli and EU-Eylea batches regarding VEGFA110 binding was observed but not expected to have relevant impact.

Although Mynzepli has highlighted similarity with EU-Eylea and CN-Eylea batches for VEGFB186 binding; Mynzepli vials batches have shown a binding slightly higher than US-Eylea batches but it is not expected to have relevant impact on efficacy and safety. In addition it has been observed a higher Galectin-1 binding for Mynzepli batches than Eylea batches respectively. Nevertheless, the role of

Galectin-1 binding in Aflibercept MoA is not thoroughly established therefore it is not expected to have any impact on safety or efficacy.

Regarding Fc related activities, lower relative binding values (FcγRIIa binding, FcγRIIb binding, FcγRIIIa binding and FcγRIIIb binding) were observed for Mynzepli batches in comparison with EU- , US- and CN-Eylea batches. However, since MoA of aflibercept does not involve effector function therefore lower relative binding values of Mynzepli batches towards those targets are unlikely to impact efficacy and safety of Mynzepli treatment.

Although some discrepancies have been underlined those are not considered to have any impact on the safety or efficacy of AVT06. Overall the demonstration of similarity performed by the applicant is considered acceptable. 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 EMEA/CHMP/BMWP/42832/2005 Rev1 guideline.

2.3.2.2. 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.

2.3.2.3. 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 cynomolgus monkeys and toxicokinetic (TK) evaluation performed as part of GLP 12-week pivotal repeat-dose toxicity study in monkeys (see section 3.2.4.6 for more details on TK data). Analytical methods were developed and sufficiently validated for the quantitation of Mynzepli and Eylea in non-human primate vitreous humor, plasma and for the detection of anti-aflibercept antibodies in non-human primate serum. Validation of the methods was conducted in compliance with GLP. Inter- and intra-assay precision and accuracy were acceptable.

The aim of the non-GLP study AVT06-PC-02 was to compare the pharmacokinetic characteristics between Mynzepli and Eylea after a single intravitreal injection (both eyes) administered to cynomolgus monkeys. There was no significant difference in VH, AH and serum pharmacokinetic parameters between genders after intravitreal injection of Mynzepli and Eylea in both eyes. The mean Cmax and AUCinf of the drug in VH, AH and serum of animals were positively correlated with the administered dose. Tmax in VH and AH ranged from 6 h to 48 h after dosing whereas Tmax in serum ranged from 24 h to 168 h after dosing.

As expected and in line with IVT administration purpose, exposures concentrations in VH and AH of animals in all groups were higher than those in serum, indicating that most of the drug was distributed in ocular tissues after vitreous injection.

PK parameters in cynomolgus monkeys were basically the same between Mynzepli and Eylea at the same dose although some differences were noted.

Comparative TK assessments were performed as part of GLP 12-week pivotal repeat-dose toxicity study in cynomolgus monkeys (please refer to sections 3.2.4.2 and 3.2.4.6 for more details).

There were no distribution, 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) of Directive 2001/83/EC and EMEA/CHMP/BMWP/42832/2005 Rev. 1 guideline).

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 has conducted a GLP-compliant comparative 12-week (plus 6 weeks recovery period) repeat dose toxicity study (AVT06-PC-03) in cynomolgus monkeys to address a request from FDA related to the initiation of a clinical study with AVT06.

Specifically, local tolerability, PK, and toxicity assessment after repeated IVT administration have been evaluated. Animals in Groups 1-5 were bilaterally treated with IVT injection of sodium chloride injection (Group 1), AVT06-aflibercept injection solution (2 mg/eye, Group 2; 4 mg/eye, Group 3), aflibercept IVT injection (2 mg/eye, Group 4; 4 mg/eye, Group 5), and the dose volume was 100, 50, 100, 50, 100 µL/eye respectively. The treatment was repeated for total 4 times (on Days 1, 29, 57 and 85) in 12 weeks with 4 weeks interval. The study continued for 6 weeks after the last dose to observe the reversibility of toxicity.

No Mynzepli (2 mg/eye or 4 mg/eye) or Eylea (2 mg/eye or 4 mg/eye) related findings were noted in clinical observations, body weight, food consumption, body temperature, electrocardiogram, blood pressure, blood oxygen saturation, haematology, coagulation, clinical chemistry, urinalysis, and T-lymphocyte subpopulation in animals in 2 and 4 mg/eye of Mynzepli and Eylea groups throughout the study. In addition, no related findings were noted in organ weights, macroscopic findings, and microscopic findings in animals in 2 and 4 mg/eye of test article and reference control article groups at the terminal necropsy (Day 88) and recovery necropsy (Day 127).

Regarding TK aspects, proof of exposure was demonstrated in all treated animals and no statistical difference was observed between genders. For Mynzepli and Eylea it was observed that a proportional increase in exposures (Cmax, AUC values) with a dose increase. No accumulation was reported after 4 IVT administrations of Mynzepli or Eylea. Lower serum exposure after repeated treatment with Mynzepli and Eylea has been demonstrated since levels in VH were found to be higher than in AH and by far higher than in serum. Overall TK parameters were considered similar between Mynzepli and Eylea at the same dosing regimen.

In addition, regarding immunogenicity a similar trend was also observed whatever the dosing strength with the formation of ADA with the same earlier onset (D28), same incidence and same titer range at 2m/eye (higher titer for Eylea was observed at 4 mg/eye).

Based on the results of Study AVT06-PC-03, a NOAEL of 4mg/eye has been set for Mynzepli and Eylea and this is acknowledged.

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.

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

In line with current recommendations, developmental and reproductive toxicity studies were not conducted to support the marketing authorisation application of Mynzepli (EMEA/CHMP/BMWP/42832/2005 Rev1). SmPC sections 4.6 and 5.3 report the results of nonclinical studies conducted with aflibercept during the development of the reference medicinal product, with the same wording.

2.3.4.6. Toxicokinetic data

Comparative TK assessments were performed as part of the GLP-compliant 12-week repeat-dose toxicity study in cynomolgus monkeys. The drug concentrations of in serum samples of all Negative Control Group animals were below the LLOQ.

Regarding TK aspects, proof of exposure was demonstrated in all treated animals and no statistical difference was observed between genders. For Mynzepli and Eylea it was observed that a proportional increase in exposures (Cmax, AUC values) with a dose increase. No accumulation was reported after 4 IVT administrations of Mynzepli or Eylea. Lower serum exposure after repeated treatment with Mynzepli and Eylea has been demonstrated since levels in VH were found to be higher (4.6 fold) than in AH and by far higher than in serum. Overall TK parameters were considered similar between Mynzepli and Eylea at the same dosing regimen.

2.3.4.7. Tolerance

Mynzepli formulation contains poloxamer 188 which has been used as a surfactant in approved biologics, including ocular products, although not in any approved products by the IVT route of administration. Therefore, to assess the tolerability of the poloxamer 188 in Mynzepli formulation, Alvotech conducted a 4-week (single dose) IVT injection tolerability GLP-compliant study (Study AVT06-PC-001) of Mynzepli vehicle in rabbits.

The objective of this study was to determine the tolerability of Mynzepli vehicle, in comparison to an Eylea® vehicle as well as 0.9% saline, when given by intravitreal injection to rabbits.

Mynzepli vehicle or Eylea vehicle did not exhibit any related findings on body weights, food consumption, clinical observations, ophthalmic examinations, tonometry, ERG or at post-mortem macroscopic ocular evaluations.

No microscopic observations associated with either of the vehicles were observed at any of the necropsy time points.

Minor vitreal haemorrhage, cells and opacities were noted but these were considered secondary to the dosing procedures but unrelated to the test materials. No vehicle-related changes were observed in IOP.

2.3.4.8. Other toxicity studies

Since Polysorbate 20, presents in Eylea, has been replaced by Poloxamer 188 in AVT06, the applicant has conducted an in vitro test (Study AVTG-AVT06-CMA-AR-002) to assess any related-impact on cell proliferation. The aim of the study was to determine the impact of Eylea- and Mynzepli batches, Eylea- and Mynzepli vehicle on cell proliferation using primary human retinal cells (HRMEC). To determine the effect of the compounds in regard of HRMEC cytotoxic effect / cell proliferation, an ATPlite Luminescence Assay were used. The assay was conducted on 96 well plates using cycloheximide as positive control (inhibition of proliferation).

Up to 19.52 µL/well, Eylea vehicle and Mynzepli vehicle, have demonstrated a similar profile with an average cell proliferation vehicle higher than 90 %. Whereas a toxic effect is observed for Eylea vehicle above 19.52 µL/well, no toxicity was noted for Mynzepli vehicle up to 53.57 µL/well. In comparison with Mynzepli vehicle elicits toxic effect at 75 µl/well.

A similar trend was observed for Eylea batches vs Mynzepli batches.

Overall, it appears that the Mynzepli vehicle does not have effect on cell viability up to 54 µL/well. This volume range is higher than physiological conditions (calculated as 7.11 µL/well). Therefore it is expected that eye treatment with 50 µL of Mynzepli will not have an additional toxic effect.

2.3.5. Ecotoxicity/environmental risk assessment

Mynzepli 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 EMEA/CHMP/SWP/4447/00 Rev. 1. An expert statement justifying the absence of an ERA has been submitted by the applicant. The applicant's justification for the lack of an ERA is considered acceptable. Aflibercept is not expected to pose a risk to the environment

2.3.6. Discussion on non-clinical aspects

The non-clinical in vitro functional activity data support the biosimilarity of Mynzepli versus the EU approved RMP, Eylea. In general, Mynzepli appears to exhibit similar VEGF-related biological activities and Fc-related biological activities as the RMP, Eylea. However, Mynzepli higher binding affinity for galectin-1 compared to Eylea and slight variability in FcRn binding affinity. Nevertheless, the role of binding in Aflibercept MoA is not thoroughly established therefore it is not expected to have any impact on safety or efficacy. In addition, MoA of aflibercept does not involve effector function therefore lower relative binding values of Mynzepli batches towards those targets are unlikely to impact efficacy and safety of Mynzepli treatment. Overall, in vitro pharmacology studies do not suggest a significant difference between Mynzepli and the RMP, EU-approved Eylea.

PK parameters in cynomolgus monkeys were basically the same between Mynzepli and Eylea at the same dose although some differences were noted. There were no distribution, 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 EMEA/CHMP/BMWP/42832/2005 Rev. 1 guideline).

The GLP-compliant comparative 12-week (plus 6 weeks recovery period) repeat dose toxicity study (AVT06-PC-03) in cynomolgus monkeys did not highlight any difference between Mynzepli and Eylea. Based on the results of Study AVT06-PC-03, a NOAEL of 4mg/eye has been set for Mynzepli and Eylea.

No genotoxicity, carcinogenicity, developmental and reproductive studies have been carried out with Mynzepli 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).

During CHMP Scientific Advice (EMA/SA/0000063900) it was agreed that a local tolerance study could be conducted to evaluate the impact of the use of poloxamer 188 in Mynzepli FP. It was considered reasonable not to administer the finished product (including aflibercept) due to the risk of inducing intraocular inflammation that could confound the safety evaluation of the Mynzepli vehicle. Dutch-Belted rabbits are considered to present a relevant animal species for the respective endpoints as this is a well-established species for ocular testing and it is also sensitive to ocular inflammation.

No adverse findings following a single bilateral intravitreal injection, of Mynzepli vehicle, Eylea vehicle or 0.9% sodium chloride (saline) to rabbits, were reported.

An overall tolerability of the Mynzepli and Eylea vehicles is considered under the test conditions and can support the use of poloxamer 188 via IVT route

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 EMEA/CHMP/SWP/4447/00 Rev. 1.

Section 4.6 is in line with the innovator product.

2.3.7. Conclusion on the non-clinical aspects

Overall, the available nonclinical in vitro studies support the MAA of Mynzepli and are in compliance with legislation from EU as well as the biosimilar relevant guidance from the EMA.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

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

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

Table 2: Tabular overview of clinical studies

Study ID	Study Objective	Participants	Study Design	Treatments/Duration	Primary Endpoint and PK, Immunogenicity Endpoints
AVT06-GL-C01	To evaluate the efficacy, safety, systemic PK and immunogenicity, of AVT06 versus EU-Eylea in participants with neovascular (wet) AMD	Treatment Naïve Neovascular (wet) AMD participants Number of participants randomized: 413. Number of participants in the PK sub-study: 40 (planned) 24 (enrolled)	Phase 3 Multicenter, randomized, double-masked, parallel group, therapeutic equivalence design	Forty-eight (48) weeks treatment duration. Overall Study Duration (excluding screening): 52 weeks. The total maximum study duration per participant is 56 weeks including screening period.	Primary endpoint • Change from baseline to week 8 in BCVA as assessed by ETDRS letter score. Secondary systemic PK, and immunogenicity endpoints [a] • **Immunogenicity** Proportion of participants testing positive for ADAs, including nAb and titers (for positive ADA) from baseline to Week 4, Week 8, Week 16, Week 24, and Week 52. • **Systemic PK** Evaluate systemic PK profile of free and bound aflibercept from baseline (Day 1 predose) to Day 1 (1 to 4 hours postdose), Day 2, Day 3, Week 4 (predose), Week 8 Day 1 (predose), Week 8 Day 1 (1 to 4 hours postdose), Week 8 Day 2, Week 8 Day 3, and Week 16 (predose).

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Bioequivalence

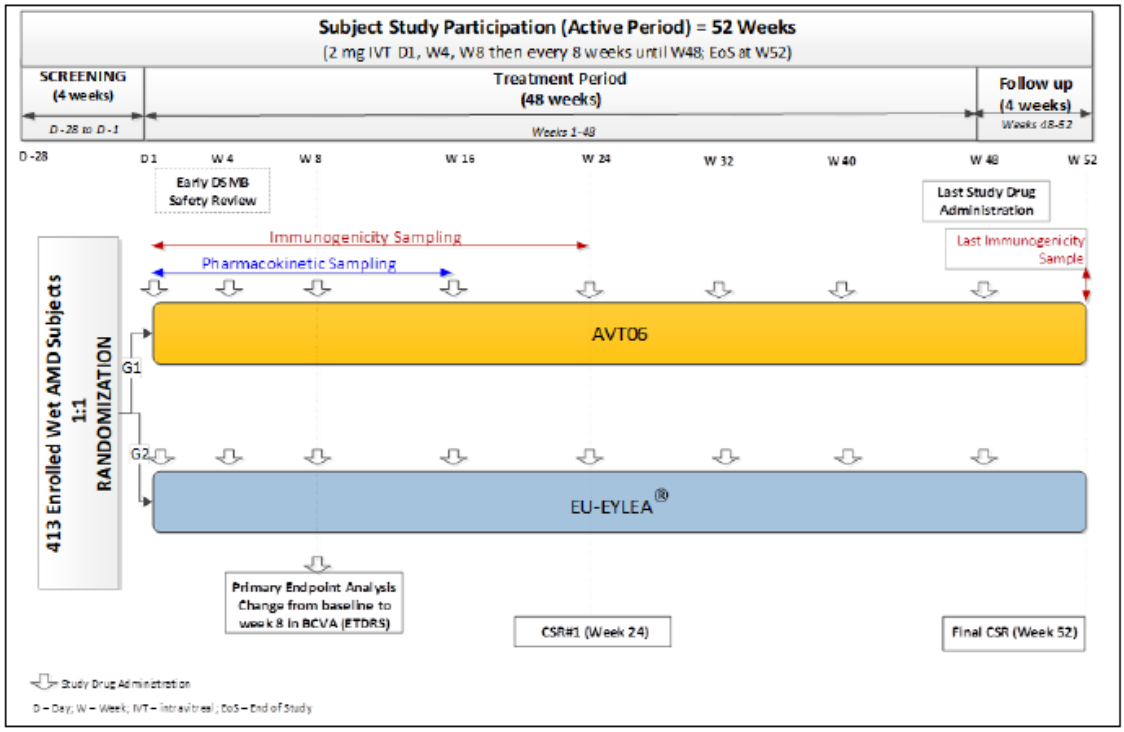
Study AVT06-GL-C01

Study AVT06-GL-C01 was a Phase 3, randomized, double-masked, parallel-group, multicenter, equivalence study evaluating the efficacy, safety, and immunogenicity of Mynzepli compared with Eylea in patients with neovascular AMD at least 50 years old. As a secondary endpoint, the study evaluated systemic PK of Mynzepli and Eylea in a subset of participants to support demonstration of no clinically meaningful differences in systemic safety of the product. The design of the study is summarised in Figure 6.

Participants received 2 mg (0.05 mL) IVT injection of Mynzepli or Eylea in their study eye every 4 weeks for 3 consecutive monthly visits (Day 1, Week 4, and Week 8), followed by IVT injections every 8 weeks throughout the remaining treatment period (at Weeks 16, 24, 32, 40, and 48).

A total of 410 participants (Mynzepli: 205; Eylea: 205) were randomly assigned to the study treatment and received at least one dose of randomized study treatment in the study eye (Mynzepli or Eylea) which is full analysis set.

Figure 1: Schema of Study AVT06-GL-C01



PK sampling and data analysis

The PK sampling was performed at Baseline (Day 1 predose), Day 1 (1 to 4 hours postdose), Day 2, Day 3, Week 4 (predose), Week 8 Day 1 (predose), Week 8 Day 1 (1 to 4 hours postdose), Week 8 Day 2, Week 8 Day 3, and Week 16 (predose).

According to the statistical analysis plan (SAP), the PK dataset is defined as all subjects recruited in the PK part who receive at least one dose of study treatment and have at least one post-treatment PK result. Systemic aflibercept concentrations were to be evaluated in a subset of approximately 40 subjects (20 subjects per treatment group) at the PK time points. The PK data were to be summarized descriptively with no formal hypothesis testing. Descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for plasma concentrations were presented by treatment group at each scheduled visit and time point.

The PK parameters evaluated comprise maximum observed concentration (Cmax) and time to maximum observed concentration (Tmax) of free and bound aflibercept.

PK results

The systemic concentrations of free and bound aflibercept were available in a subset of 24 (5.8%) patients (8 [3.9%] and 16 [7.8%] patients in the Mynzepli and Eylea groups, respectively).

Figure 2 : Free Aflibercept Arithmetic Mean ± SD Concentration-Time Profiles at Day 1 and Week 8 per Treatment.

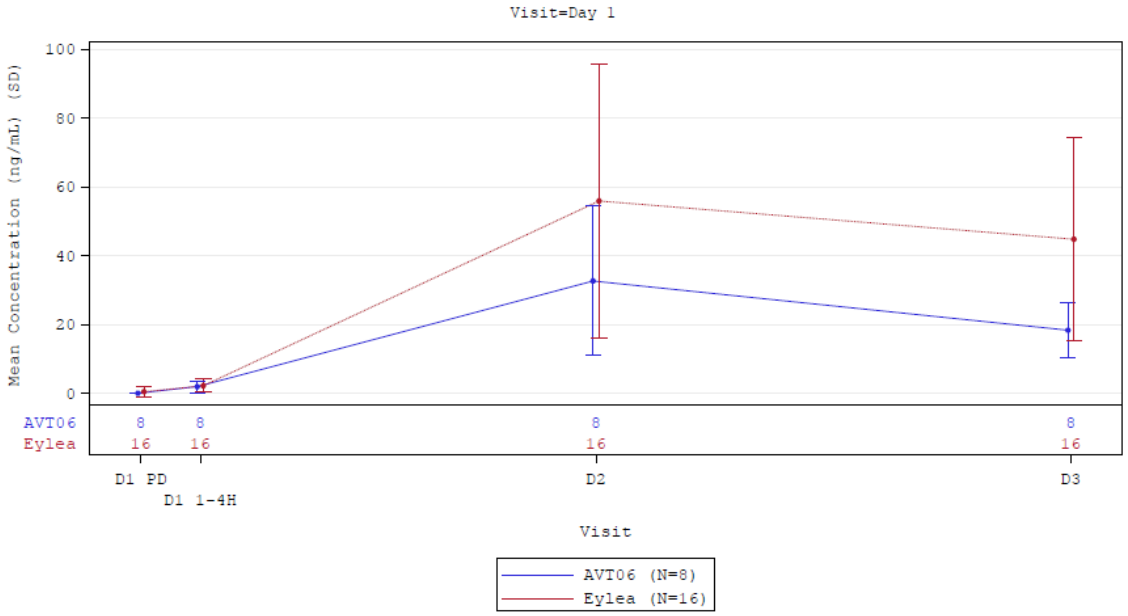


Figure 3: Free Aflibercept Arithmetic Mean ± SD Concentration-Time Profiles at Day 1 and Week 8 per Treatment.

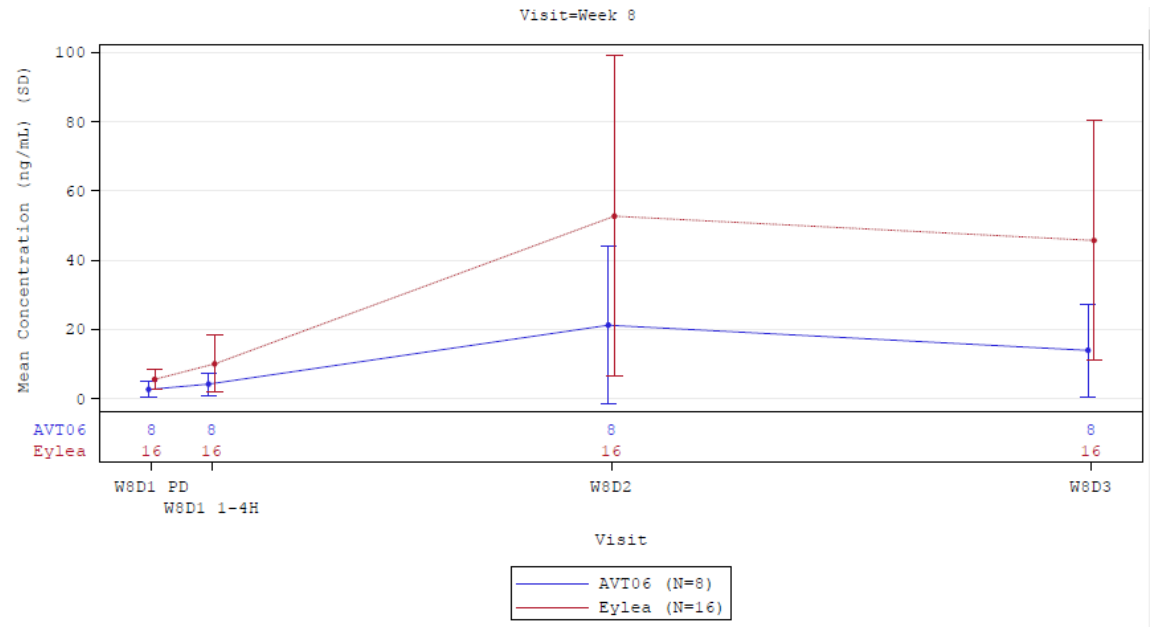


Figure 2 and Figure 3 show that following mean peak serum free aflibercept concentrations at day 1 (first IVT injection) and Week 8 (3rd injection), the serum concentrations decreased slowly, and the slopes of the mean elimination phase were similar across the treatment groups. Serum concentrations were still measurable at Day 3 after injection.

The free aflibercept concentrations by treatment and nominal PK sampling timepoint are summarized in Table 3. Concentrations that were below the LLOQ were set to 0.5*LLOQ (that is 1 ng/mL for free and 0.125 ng/mL for total).

At Day 1, Cmax free aflibercept mean (SD) was 33.09 (21.145) ng/mL and 59.51 (38.131) ng/mL in the Mynzepli and Eylea groups, respectively. Tmax free aflibercept median (min-max) was 24.4 (23.250 – 46.667) hours in the Mynzepli group and 23.3 (1.450 – 48.383) hours in Eylea group. At

Week 8, Cmax free mean (SD) was 21.60 (22.496) ng/mL and 56.36 (45.749) ng/mL in the Mynzepli and Eylea groups, respectively. Tmax free median (min-max) was 22.14 (2.083 - 48.700) hours in the Mynzepli group and 22.48 (1.500 – 48.667) hours in Eylea group. Summary of serum free and bound aflibercept PK parameters (Cmax and Tmax) by treatment is provided in Table 3 and Table 4 (below)**.** Graphical summaries of concentration-time profiles of free and bound aflibercept from day 1 to Week 16 are presented in Figure 9 and Figure 10 in linear scale, respectively.

Figure 4: Arithmetic Mean ± SD Serum Concentration-Time Profiles of Free Aflibercept per Treatment and Visit in Study AVT06-GL-C01.

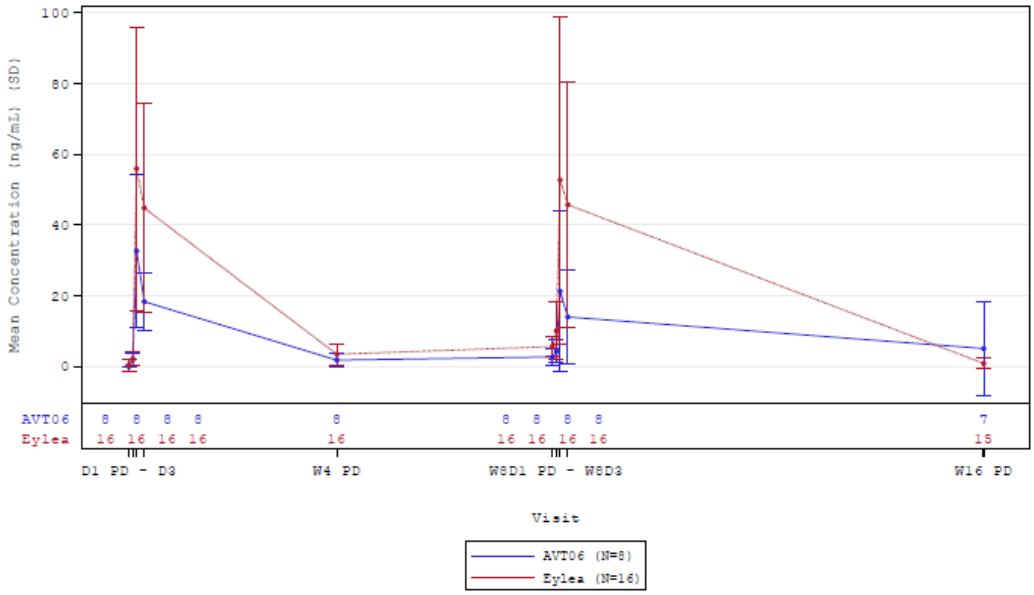


Figure 5: Arithmetic Mean ± SD Concentration-Time Profiles of Bound Aflibercept per Treatment and Visit in Study AVT06-GL-C01.

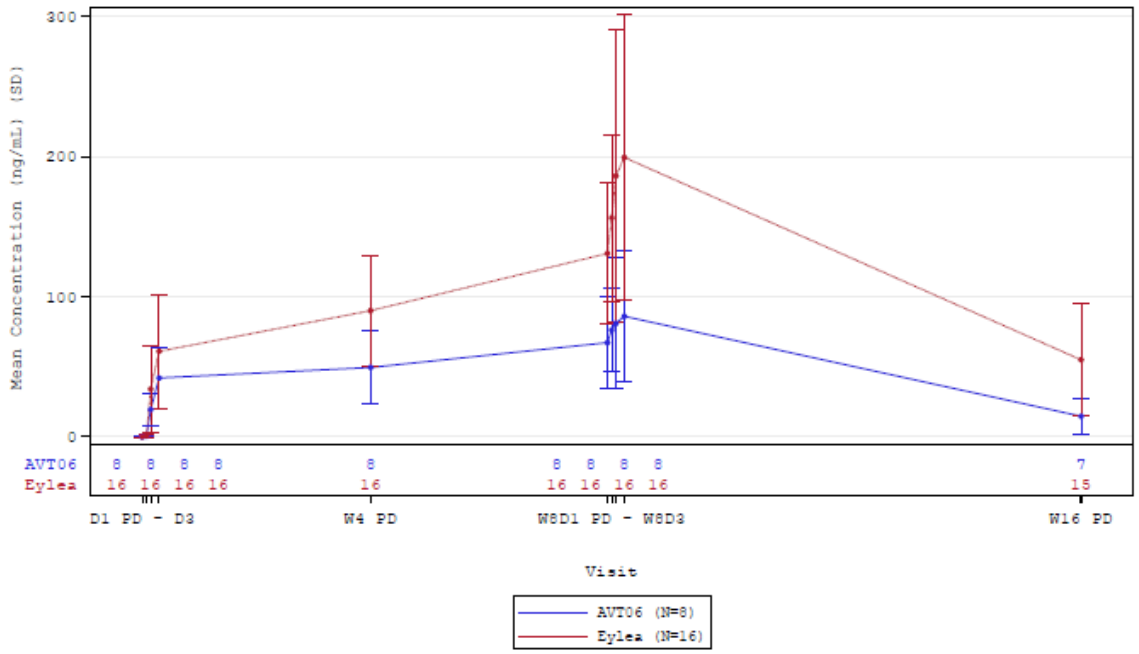


Table 3: Summary of Serum Free and Bound Aflibercept Concentrations by Treatment and Nominal Pharmacokinetic Sampling Timepoint (Pharmacokinetic Analysis Set) in Study AVT06-GL-C01.

Parameter	Visit, Timepoint	Statistic	AVT06 (N=8)	Eylea (N=16)	Total (N=24)
Concentration of free aflibercept (ng/ml)	Day 1, predose	n	8	16	24
		Mean (SD)	0.000 (0.0000)	0.420 (1.6800)	0.280 (1.3717)
		CV%	-	400.00	489.90
		Median	0.000	0.000	0.000
		Min, Max	0.00, 0.00	0.00, 6.72	0.00, 6.72
		Geometric Mean	-	6.720	6.720
		Geometric CV%	-	-	-
	Day 1, 1-4 hours postdose	n	8	16	24
		Mean (SD)	1.919 (1.7106)	2.171 (1.8719)	2.087 (1.7862)
		CV%	89.15	86.21	85.58
		Median	1.000	1.000	1.000
		Min, Max	1.00, 5.01	1.00, 6.01	1.00, 6.01
		Geometric Mean	1.469	1.616	1.566
		Geometric CV%	81.51	86.25	82.57
	Day 2	n	8	16	24
		Mean (SD)	32.625 (21.7384)	55.900 (39.9682)	48.142 (36.2113)
		CV%	66.63	71.50	75.22
		Median	32.900	48.950	47.700
		Min, Max	1.00, 61.20	1.00, 142.00	1.00, 142.00
		Geometric Mean	20.942	33.310	28.536
		Geometric CV%	228.05	278.73	255.89
Concentration of free aflibercept (ng/ml) (continued)	Day 3	n	8	16	24
		Mean (SD)	18.323 (8.0279)	44.769 (29.4350)	35.953 (27.3286)
		CV%	43.81	65.75	76.01
		Median	19.400	40.900	30.200
		Min, Max	2.38, 25.70	1.00, 107.00	1.00, 107.00
		Geometric Mean	15.335	27.958	22.886
		Geometric CV%	93.34	245.38	192.09

Parameter	Visit, Timepoint	Statistic	AVT06 (N=8)	Eylea (N=16)	Total (N=24)
	Week 4, predose	n	8	16	24
		Mean (SD)	1.794 (1.7423)	3.451 (2.9538)	2.899 (2.6928)
		CV%	97.13	85.59	92.89
		Median	2.220	3.670	2.450
		Min, Max	0.00, 5.01	0.00, 9.27	0.00, 9.27
		Geometric Mean	2.716	4.613	3.909
		Geometric CV%	35.81	46.67	50.58
	Week 8 Day 1, predose	n	8	16	24
		Mean (SD)	2.703 (2.3052)	5.630 (2.8337)	4.654 (2.9734)
		CV%	85.30	50.33	63.89
		Median	2.325	5.080	4.575
		Min, Max	0.00, 6.70	0.00, 11.00	0.00, 11.00
		Geometric Mean	3.253	5.522	4.748
		Geometric CV%	50.98	45.38	53.16
Concentration of free aflibercept (ng/ml) (continued)	Week 8 Day 1, 1-4 hours postdose	n	8	16	24
		Mean (SD)	4.251 (3.2302)	10.094 (8.1938)	8.146 (7.4079)
		CV%	75.98	81.18	90.94
		Median	2.845	7.110	6.840
		Min, Max	1.00, 9.57	2.63, 35.40	1.00, 35.40
		Geometric Mean	3.158	8.221	5.976
		Geometric CV%	105.82	68.01	99.57
	Week 8 Day 2	n	8	16	24
		Mean (SD)	21.244 (22.8052)	52.713 (46.2847)	42.223 (42.2500)
		CV%	107.35	87.80	100.06
		Median	12.900	48.350	35.550
		Min, Max	1.00, 54.20	5.09, 146.00	1.00, 146.00
		Geometric Mean	8.668	32.106	20.751
		Geometric CV%	394.89	166.26	270.30
	Week 8 Day 3	n	8	16	24
		Mean (SD)	13.986 (13.4333)	45.703 (34.5344)	35.131 (32.6494)
		CV%	96.05	75.56	92.94
		Median	12.435	47.900	25.700

Parameter	Visit, Timepoint	Statistic	AVT06 (N=8)	Eylea (N=16)	Total (N=24)
		Min, Max	1.00, 35.40	5.13, 109.00	1.00, 109.00
		Geometric Mean	6.865	29.828	18.280
		Geometric CV%	286.34	151.74	246.24
Concentration of free aflibercept (ng/ml) (continued)	Week 16, predose	n	7	15	22
		Mean (SD)	5.071 (13.4177)	0.867 (1.5790)	2.205 (7.5576)
		CV%	264.58	182.05	342.75
		Median	0.000	0.000	0.000
		Min, Max	0.00, 35.50	0.00, 4.46	0.00, 35.50
		Geometric Mean	35.500	3.097	5.044
		Geometric CV%	-	38.06	162.42
Concentration of bound aflibercept (ng/ml)	Day 1, predose	n	8	16	24
		Mean (SD)	0.0000 (0.00000)	0.2175 (0.87000)	0.1450 (0.71035)
		CV%	-	400.000	489.898
		Median	0.0000	0.0000	0.0000
		Min, Max	0.000, 0.000	0.000, 3.480	0.000, 3.480
		Geometric Mean	-	3.4800	3.4800
		Geometric CV%	-	-	-
	Day 1, 1-4 hours postdose	n	8	16	24
		Mean (SD)	0.4425 (0.61350)	0.7455 (1.17293)	0.6445 (1.01640)
		CV%	138.643	157.334	157.704
		Median	0.1250	0.2700	0.1475
		Min, Max	0.080, 1.720	0.125, 4.730	0.080, 4.730
		Geometric Mean	0.2230	0.3515	0.3020
		Geometric CV%	163.343	173.605	169.034
Concentration of bound aflibercept (ng/ml) (continued)	Day 2	n	8	16	24
		Mean (SD)	19.5000 (12.00452)	34.1122 (31.01960)	29.2415 (26.84962)
		CV%	61.562	90.934	91.820
		Median	17.3500	30.6000	24.7000

Parameter	Visit, Timepoint	Statistic	AVT06 (N=8)	Eylea (N=16)	Total (N=24)
		Min, Max	4.600, 39.800	0.125, 131.000	0.125, 131.000
		Geometric Mean	16.0958	18.3378	17.5578
		Geometric CV%	79.886	374.281	241.360
	Day 3	n	8	16	24
		Mean (SD)	42.0675 (21.79726)	61.0478 (40.81241)	54.7210 (36.25512)
		CV%	51.815	66.853	66.254
		Median	43.0500	56.5000	53.3000
		Min, Max	6.640, 72.400	0.125, 172.000	0.125, 172.000
		Geometric Mean	34.8069	35.0021	34.9369
		Geometric CV%	89.336	446.918	277.487
	Week 4, predose	n	8	16	24
		Mean (SD)	49.5400 (26.40397)	90.0800 (39.45847)	76.5667 (40.10857)
		CV%	53.298	43.804	52.384
		Median	54.2200	89.8950	69.2900
		Min, Max	5.370, 94.590	3.600, 161.490	3.600, 161.490
		Geometric Mean	39.3330	74.0062	59.9466
		Geometric CV%	109.766	107.422	114.097
Concentration of bound aflibercept (ng/ml) (continued)	Week 8 Day 1, predose	n	8	16	24
		Mean (SD)	67.2600 (32.70161)	130.9138 (49.91197)	109.6958 (53.75606)
		CV%	48.620	38.126	49.005
		Median	70.8200	107.1350	98.2250
		Min, Max	23.380, 119.300	65.660, 267.350	23.380, 267.350
		Geometric Mean	59.0970	123.3692	96.5294
		Geometric CV%	63.277	35.802	59.918
	Week 8 Day 1, 1-4 hours postdose	n	8	16	24
		Mean (SD)	76.2863 (30.05485)	156.2938 (59.68907)	129.6246 (63.89685)
		CV%	39.397	38.190	49.294
		Median	72.5650	141.6750	127.0400

Parameter	Visit, Timepoint	Statistic	AVT06 (N=8)	Eylea (N=16)	Total (N=24)
		Min, Max	33.800, 126.440	64.280, 300.600	33.800, 300.600
		Geometric Mean	71.0345	146.1833	114.9269
		Geometric CV%	43.159	39.542	55.381
	Week 8 Day 2	n	8	16	24
		Mean (SD)	80.9625 (46.85897)	186.2244 (104.07619)	151.1371 (101.49787)
		CV%	57.877	55.888	67.156
		Median	91.7000	151.3750	124.8050
		Min, Max	1.950, 140.000	79.200, 491.000	1.950, 491.000
		Geometric Mean	52.7536	165.5136	113.0593
		Geometric CV%	249.187	51.262	136.982
Concentration of bound aflibercept (ng/ml) (continued)	Week 8 Day 3	n	8	16	24
		Mean (SD)	86.0588 (47.01360)	199.4219 (101.81593)	161.6342 (102.04622)
		CV%	54.630	51.056	63.134
		Median	110.1500	158.3150	125.1350
		Min, Max	2.160, 129.900	100.170, 470.200	2.160, 470.200
		Geometric Mean	56.8630	179.2057	122.2300
		Geometric CV%	242.658	49.195	134.645
	Week 16, predose	n	7	15	22
		Mean (SD)	14.7129 (12.94727)	54.9727 (40.41765)	42.1627 (38.79856)
		CV%	88.000	73.523	92.021
		Median	15.1000	37.6000	29.5000
		Min, Max	0.530, 30.300	15.800, 162.540	0.530, 162.540
		Geometric Mean	6.9278	43.6991	24.3202
		Geometric CV%	372.470	78.945	233.607

Table 4: Serum Free and Bound Aflibercept PK parameters (Cmax and Tmax) by Treatment in Study AVT06-GL-C01.

Parameter	Visit	Statistic	AVT06 (N=8)	Eylea (N=16)	Total (N=24)
Maximum observed concentration of free aflibercept (ng/ml) C_{max} free	Day 1	n	8	16	24
		Mean (SD)	33.09 (21.145)	59.51 (38.131)	50.70 (35.302)
		Median	32.90	52.85	48.95
		Min, Max	2.4, 61.2	1.0, 142.0	1.0, 142.0
	Week 8	n	8	16	24
		Mean (SD)	21.60 (22.496)	56.36 (45.749)	44.77 (42.417)
		Median	13.54	53.35	41.45
		Min, Max	1.0, 54.2	5.4, 146.0	1.0, 146.0
Maximum observed concentration of bound aflibercept (ng/ml) C_{max} bound	Day 1	n	8	16	24
		Mean (SD)	42.07 (21.797)	61.05 (40.812)	54.72 (36.255)
		Median	43.05	56.50	53.30
		Min, Max	6.6, 72.4	0.1, 172.0	0.1, 172.0
	Week 8	n	8	16	24
		Mean (SD)	95.22 (37.630)	204.40 (103.400)	168.00 (100.835)
		Median	110.15	170.26	133.82
		Min, Max	39.1, 140.0	103.4, 491.0	39.1, 491.0
Time to maximum observed concentration of free aflibercept (hours) T_{max} free	Day 1	n	8	16	24
		Mean (SD)	29.7042 (10.37614)	27.9406 (15.25417)	28.5285 (13.61039)
		Median	24.4000	23.3333	23.6500
		Min, Max	23.250, 46.667	1.450, 48.383	1.450, 48.383
	Week 8	n	8	16	24
		Mean (SD)	20.7542 (14.61861)	25.4854 (11.42583)	23.9083 (12.46483)
		Median	22.1417	22.4833	22.2500
		Min, Max	2.083, 48.700	1.500, 48.667	1.500, 48.700
Time to maximum observed concentration of bound aflibercept (hours) T_{max} bound	Day 1	n	8	16	24
		Mean (SD)	47.7417 (1.06760)	44.1365 (11.24391)	45.3382 (9.26349)
		Median	47.8250	46.7833	47.0000
		Min, Max	46.283, 49.333	2.250, 50.167	2.250, 50.167
	Week 8	n	8	16	24
		Mean (SD)	32.8375 (20.97358)	30.5760 (19.68916)	31.3299 (19.69491)
		Median	45.8667	44.5500	44.9500
		Min, Max	1.950, 49.000	0.000, 48.667	0.000, 49.000

2.4.2.2. Pharmacodynamics

Mechanism of action

Aflibercept is a dimeric glycoprotein with a protein molecular weight of 96.9 kilo Daltons (kDa). It contains approximately 15% glycosylation to give a total molecular weight of 115 kDa.

Aflibercept is a recombinant human soluble fusion protein consisting of sequences derived from the extracellular domains of VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2) fused to the Fc region of IgG1. Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.

Primary and Secondary pharmacology

Not applicable

Immunological events

Immunological events related to Mynzepli were assessed during the pivotal clinical Phase 3 study (AVT06-GL-C01) in participants with neovascular (wet) AMD as a secondary objective.

Antibodies (ADAs and nAb) directed to Mynzepli were evaluated in serum samples collected from all participants according from Baseline to Week 4, Week 8, Week 16, Week 24, and Week 52. However, only data up to 24 weeks are available.

In the scientific advice (EMA/SA/0000063900), it was concluded that in terms of immunogenicity assessment for the biosimilar products, the wet AMD patient population is agreed as a sensitive patient population. The number of ADAs and nAbs (i.e., positive, or negative) to aflibercept were globally similar across groups until Week 24. Regarding ADA, at baseline, 24 patients were tested positive (Mynzepli: 10 patients; Eylea: 14 patients) versus 82 patients in total at Week 24 (Mynzepli: 34 patients; Eylea: 48 patients). Regarding nAb, at baseline, 2 patients were tested positive, both in Eylea group, versus 39 patients in total at Week 24 (Mynzepli: 17 patients; Eylea: 22 patients).

The observed incidence of ADA positive subjects in this pivotal study, at baseline and up to 24 weeks, was significantly higher compared to the historical data presented in Eylea SPC (ADA positive patients lower than 5%). The applicant provided justification for the high ADA incidence in terms of the appropriateness of the cut-points and assay sensitivity. The assay has been shown to be extremely sensitive. It was proved that the high incidence of ADA and NAb positive participants in the pivotal study was due to the high sensitivity of the assays. The levels of antibodies were however very low.

The observed higher incidence of ADA positive subjects was also not associated with a higher incidence of immune-mediated TEAEs.

Table 5: Number and Proportion of Participants Testing Positive and Negative for ADA and nAb by Treatment Group (SAF)

Parameter Value	Visit	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
ADA					
Positive	Baseline	n	10	14	24
		Proportion (%)	5.0	7.0	6.0
Negative		n	189	186	375
		Proportion (%)	95.0	93.0	94.0
Positive	Week 4	n	55	87	142
		Proportion (%)	27.5	43.3	35.4
Negative		n	145	114	259
		Proportion (%)	72.5	56.7	64.6
Positive	Week 8	n	88	116	204
		Proportion (%)	44.0	58.6	51.3
Negative		n	112	82	194
		Proportion (%)	56.0	41.4	48.7
Positive	Week 16	n	46	69	115
		Proportion (%)	23.4	36.3	29.7
Negative		n	151	121	272
		Proportion (%)	76.6	63.7	70.3
Positive	Week 24	n	34	48	82
		Proportion (%)	17.3	24.9	21.1
Negative		n	162	145	307
		Proportion (%)	82.7	75.1	78.9
Positive	Up to Week 24 [a]	n	109	140	249
		Proportion (%)	53.2	68.3	60.7
Negative		n Proportion (%)	96 46.8	65 31.7	161 39.3
nAb					
Positive	Baseline	n	0	2	2
		Proportion (%)	0	14.3	8.3
Negative		n	10	12	22
		Proportion (%)	100.0	85.7	91.7
Positive	Week 4	n	40	75	115
		Proportion (%)	72.7	86.2	81.0
Negative		n	15	12	27
		Proportion (%)	27.3	13.8	19.0
Positive	Week 8	n	73	103	176
		Proportion (%)	83.0	88.8	86.3
Negative		n	15	13	28
		Proportion (%)	17.0	11.2	13.7
Positive	Week 16	n	29	45	74
		Proportion (%)	63.0	65.2	64.3
Negative		n	17	24	41
		Proportion (%)	37.0	34.8	35.7
Positive	Week 24	n	17	22	39
		Proportion (%)	50.0	45.8	47.6
Negative		n	17	26	43
		Proportion (%)	50.0	54.2	52.4
Positive	Up to Week 24 [b]	n	87	120	207
		Proportion (%)	79.8	85.7	83.1
Negative		n	22	20	42
		Proportion (%)	20.2	14.3	16.9

n: number of subjects; ADA: Anti-drug Antibodies; nAb: Neutralizing ADA.
The proportion of ADA positive/negative is based on the number of subjects per treatment group with ADA assessed at the specified visit; The proportion of nAb positive/negative is based on the number of ADA positive subjects per treatment group at the specified visit.

[a] Subjects who had a positive ADA result at any visit up to Week 24 contribute towards the positive count. Subjects who only had negative ADA results at visits up to Week 24 contribute towards the negative count. The proportion is based on the number of subjects per treatment group with ADA assessed up to Week 24.

[b] Subjects who had a positive nAb result at any visit up to Week 24 contribute towards the positive count. Subjects who only had negative nAb results at visits up to Week 24 contribute towards the negative count. The proportion is based on the number of subjects per treatment group who had a positive ADA result at any visit up to Week 24.

Table 6: Summary of Immunogenicity ADA Titers by Treatment Group (SAF)

Visit	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
Baseline	n	10	14	24
	Mean (SD)	7.9 (12.89)	3.4 (4.43)	5.3 (9.02)
	Median	1.0	1.0	1.0
	Q1, Q3	1.0, 8.0	1.0, 4.0	1.0, 6.0
	Min, Max	1, 32	1, 16	1, 32
Week 4	n	55	87	142
	Mean (SD)	2.1 (3.08)	1.9 (2.19)	1.9 (2.56)
	Median	1.0	1.0	1.0
	Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
	Min, Max	1, 16	1, 16	1, 16
Week 8	n	88	116	204
	Mean (SD)	2.2 (3.56)	1.9 (2.24)	2.0 (2.88)
	Median	1.0	1.0	1.0
	Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
	Min, Max	1, 32	1, 16	1, 32
Week 16	n	46	69	115
	Mean (SD)	2.5 (5.08)	1.9 (2.32)	2.2 (3.67)
	Median	1.0	1.0	1.0
	Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
	Min, Max	1, 32	1, 16	1, 32
Week 24	n	34	48	82
	Mean (SD)	2.3 (3.61)	2.4 (3.67)	2.4 (3.62)
	Median	1.0	1.0	1.0
	Q1, Q3	1.0, 2.0	1.0, 2.0	1.0, 2.0
	Min, Max	1, 16	1, 16	1, 16

*n: number of subjects; SD: standard deviation; Q1: 1st Quartile; Q3: 3rd Quartile; min: minimum; max: maximum; ADA: Anti-drug Antibodies. Titers that are below the lower limit of quantification (LLOQ) are set to 0.5*LLOQ for the computation of descriptive statistics.*

2.4.3. Discussion on clinical pharmacology

Analytical methods

a) PK assays (free and total aflibercept):

Two immunoassays were developed and validated to quantify total and free aflibercept serum concentrations in samples drawn from patients treated with Mynzepli or Eylea within the clinical Phase 3 Study AVT06-GL-C01. These methods apply a sandwich assay on the MSD electrochemiluminescence platform. The quantification range is 2.0 to 200 ng/ mL and 0.25 to 200 ng/mL for free and total aflibercept, respectively. Overall, the used assays appear adequate and comply with acceptance criteria as outlined in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009

Rev. 1 Corr. 2**). Additional long-term stability data were requested. The applicant provided an updated validation assay (Validation-report N-A-IMM-21-026-Amendment-02), extending the long-term stability of the assay up to 631 days at - 75°C±15°C, covering thus the storage duration of PK samples of study AVT06-GL-C01 (up to 622 days after collection).

b) ADA and NAb assays:

ADAs to aflibercept were determined using a bridging assay based on MSD ECL technology and three-tiered approach (screening, confirmation and titration). Antigenic equivalence was demonstrated. The assay was able to measure ADAs in presence of the circulating drug, the drug tolerance was 250 ng/mL at LPC level and >2 µg/ml at HPC and MPC levels for both products, that is acceptable because concentrations of the circulating drug were lower than 250 ng/mL in most of study samples. Target (VEGF) interference was not observed. It was decided in agreement with the study plan that the validated CP would be used in the study. When the validated CP was applied to 96 pre-dose samples the false-positive rate (FPR) was within the acceptable range of 2 to 11 % (it was 4.2 %). Then 9.1 % samples were screened positive but not confirmed positive in the study out of 1999 study samples. The cut points were set correctly producing the appropriate FPR. Mean assay screening sensitivity was calculated to be 0.29 ng/mL and the mean assay confirmatory sensitivity was calculated to be 0.49 ng/mL. The assays seem to be very sensitive. The LPC concentrations for screening and confirmatory assay were appropriately determined to produce a positive result above the CP but to generate a 1 % rejection rate.

The samples confirmed positive in the ADA assay were analyzed for neutralizing antibodies. NAbs were assessed by the competitive ECL assay using biotinylated Mynzepli as a capture antigen and Sulfo-Tag labeled VEGF to compete with NAbs. When validation screening and confirmation cutpoints were applied to the data, the FPR of 0.7 % which is close to the target value of 1 % was obtained. The in-study CP (in disease-state matrix) was determined using baseline samples of human individuals in the study. It was decided that validation CP would be used for controls while the in-study CP would be used to evaluate the study samples. Both validation and in study values of % inhibition for CP (5.7 % and 6.3%, respectively) were very low. This means that with a signal inhibition of only about 6%, the sample is considered positive, underlining the sensitivity of the method. A concentration of 279 ng/mL was designated as the method sensitivity. It is acceptable assay sensitivity for neutralization assays which may not achieve that level of sensitivity as the ADA assays. (Originally, a concentration of 279 ng/mL was considered for LPC, but the drug tolerance test was inconclusive at this concentration of 279 ng/ml for levels of a drug expected in the study samples and therefore it was concluded that 500 ng/mL would be used as a LPC instead of a MPC).

Overall, the screening cut points for both ADA and NAb assays were set correctly producing false positive rate between recommended 2 and 11 %. The LPC levels were determined to produce a positive result above the CP but generate a 1 % rejection rate but had to be elevated during the study due to frequent failures, confirming that there was an effort to create a balance between false negatives and false positives and that false positivity would not be the reason for the higher ADA incidence. The ADA assay was very sensitive. The NAb assay was also adequately sensitive with CCP of 6 % inhibition only.

In summary, the provided immunogenicity data appears conflicting with historical data for aflibercept products. Indeed, a high percentages of patients in the study were tested positive for ADA (53% and 68% for Mynzepli and Eylea, respectively) versus the proportion of patients with ADA incidences known to be low (2.2 à 4.4%) up to 96 weeks of treatment with the reference product Eylea (Please refer to SmpC). The applicant provided justification of these results in terms of the appropriateness of the cut-points and assay sensitivity. It is agreed that the screening and confirmatory cut points were set correctly producing the appropriate and recommended FPR between 2 and 11 %. Moreover, correction

factor of 1.118 for the calculation of the plate specific screening cut point was very low (a very small signal change led to a determination of positivity). The assay was very sensitive with a much lower sensitivity than desirable 100 ng/mL. Although the incidence of ADA positive subjects was higher than reported for Eylea, the antibody levels (titres) were very low. Apparently, the method used for Eylea years ago was unable to detect such low levels of antibodies. LBA methods are not reliably comparable to each other. All of these arguments fit together and confirm that the high sensitivity of the assays is behind the increased incidence of ADA and NAb positive participants (with very low levels of antibodies) in the pivotal study.

Pharmacokinetics

It is generally agreed that a conventional Phase I PK study on healthy volunteers is not eligible for the comparative evaluation of the proposed biosimilar to the reference EU-Eylea given the unfavourable risk/benefit profile, the negligible and highly variable systemic concentrations of aflibercept following IVT administration. Instead, a supportive assessment of a systemic exposure on a subset of participants within a pivotal phase III study (AVT06-GL-C01) primarily designed to demonstrate equivalent efficacy in patients with wet AMD is considered more appropriate.

A systemic PK profile evaluation was performed on the target population as a secondary objective to demonstrate that there are no major differences in systemic exposure between Mynzepli and EU-Eylea and to rule out any potential concerns from a safety perspective.

Serum free and bound aflibercept concentrations were evaluated at baseline (Day 1 predose), Day 1 (1 to 4 hours postdose), Day 2, Day 3, Week 4 (predose), Week 8 Day 1 (predose), Week 8 Day 1 (1 to 4 hours postdose), Week 8 Day 2, Week 8 Day 3, and Week 16 (predose). The PK parameters comprised Cmax and Tmax of free and bound aflibercept. The PK data are summarized for descriptive evaluation with no formal hypothesis testing between the test and reference products. This is considered acceptable.

The overall PK population consisted of 24 (8 in the Mynzepli and 16 in the Eylea group). Compared to the 40 participants originally planned for PK dataset, the resulting number of included patients is considerably small and, moreover, unevenly distributed between the treatment arms. A summary of demographic and general baseline characteristics for the PK sub-population was provided by the applicant indicating a comparable distribution of characteristics between the two treatment groups. A non-zero pre-dose concentration of "free" and "total" aflibercept was detected in one study participant (#250302) for day D1. No prior ocular medication or other ocular medical history was reported for the affected subject and the finding could not be explained by clinical or bioanalytical investigation. Though not resolved, this issue is not considered to question the similarity between Mynzepli and Eylea and is no further pursued. In summary, considering the small number of patients included in the PK dataset, particularly for the Mynzepli product of interest (n=8) the available data should be interpreted with caution.

As per the provided results, plasma aflibercept levels after IVT administration were generally low in patients. The C_{max} of free aflibercept on Day 1 was 33.09 (21.145) ng/ml and 59.51 (38.131) ng/ml in Mynzepli group and Eylea group, respectively and the C_{max} of free aflibercept on Week 8 was 21.60 (22.496) ng/ml and 56.36 (45.749) ng/ml in Mynzepli group and Eylea group, respectively. These findings are expected and appear comparable to data already known (Please refer to paragraph 5.2 of the Eylea's label; mean free aflibercept Cmax values in the range of range of 0.03 to 0.05 µg/L [30 to 50 ng/mL] with individual values not exceeding 0.14 µg/L).

While both Mynzepli and Eylea treatments present similar PK profile, the measured concentrations for both free and bound aflibercept from day 1 to Week 16 (4^{th} injection) are on average lower in the Mynzepli group. This is illustrated by the mean Cmax free of 33.1 and 21.6 ng/mL on Week 0 (day 1-

3) and on Week 8 (day 1-3), respectively for the Mynzepli group (maximum values 54.2 and 61.2 ng/mL, respectively), versus mean Cmax free of 59.5 and 56.4 ng/mL, respectively (maximum values at 142 and 146 ng/mL, respectively) for Eyela. Furthermore, the provided data do not indicate any trend for accumulation of free aflibercept after repeated administration in both treatment groups (mean Week16, predose concentrations of 5.07 and 0.86 ng/mL, respectively). High variability was observed for both groups, with CV% >75% for all time points ranging from 75.1 to 264.5%, except for day2 and 3 of Week 0 (CV% from 43.8 to 71.5%). Finally, median Tmax ranged from 20.7 to 47.8 hours post dose and was comparable between products, indicating a relatively fast systemic diffusion of aflibercept after IVT injection.

In conclusion, the low plasma concentrations of free aflibercpet indicate no relevant systemic exposure and no trend for accumulation following 2 mg/0.5 mL Mynzepli IVT repeated administration according to the recommended dosing schema. Again, the very limited PK data should be regarded only for descriptive purpose and render a formal comparison between treatments (Mynzepli and Eylea) futile.

Impact of ADA on PK

The applicant was asked to further investigate the impact of immunogenicity on PK. The applicant provided, a tabulated and graphical analysis of the systemic exposure of aflibercept by ADA and NAb status. Overall, no significant difference in free aflibercept serum exposure is observed between the two subgroups of patients with and without ADA and Nab up to Week 16. However, this conclusion should be regarded with caution as derived from a small numbers of patients in each group (n= 8 and 16 for Mynzepli and Eylea, respectively).

Pharmacodynamics

No dedicated comparative pharmacodynamics (PD) investigations have been performed as part of the clinical biosimilarity exercise. This is acceptable for this biosimilar application since it relies on the information already known from the reference product.

Immunological events

The assessment of immunogenicity was performed as a part of the main Phase III study (AVT06-GL-C01). As agreed in the scientific advice (EMA/SA/0000063900), the wet AMD patient population is considered a sensitive patient population for the purpose. Blood samples were planned to be collected from all participants at Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24 and at Week 52 (EOS visit). So far, however, only data up to Week 24 have been provided.

At baseline, a positive ADA response was reported in 10 (5%) out of 205 patients and 14 (7%) out of 205 patients with available results in the Mynzepli and Eylea treatment groups, respectively.

In both treatment groups, the frequency of ADA and nAb development increased up to Week 8 and then decreased up to Week 24. The incidence of ADAs was lower in Mynzepli treatment group during the study, ranging between 5% (at baseline) and 44.0% (at Week 8) compared to a range between 7% (at baseline) and 58.6% (at Week 8) in Eylea treatment group, but these differences are not considered significant.

The frequency of nAb increased and decreased during the study in a similar manner to that of ADA. There was no patient (0%) tested positive for nAb in Mynzepli treatment group at baseline and 14.3% patients tested positive in Eylea group. At weeks 8 and 24, the incidences of nAB were 83.0% and 50.0% in Mynzepli group and 88.8% and 45.8% in Eylea group, respectively.

The reported ADA titers were very low for both treatment groups.

Overall, it can be concluded that the incidence of ADAs and nAbs was comparable between the two treatment groups. However, compared to previously assessed immunogenicity data for Eylea from

other studies, the incidence of ADAs and nAbs in this study was considerably higher for both test and reference product, with 53.2% and 68.3%, respectively tested positive for ADA after 24 weeks and around a half (50% and 45.8%, respectively) of whom positive for Nab. The applicant was requested to discuss the significantly high observed incidence of ADA positive subjects and high percentage of antibodies with neutralizing capacity in the pivotal study, at baseline and up to 24 weeks. These results are in contrast with historical data presented in Eylea SPC (ADA positive patients lower than 5%). The applicant provided justification for the high ADA incidence in terms of the appropriateness of the cut-points and assay sensitivity. The assay has been shown to be extremely sensitive. It was proved that the high incidence of ADA and NAb positive participants in the pivotal study was due to the high sensitivity of the assays. The levels of antibodies were however very low.

The observed higher incidence of ADA positive subjects was also not associated with a higher incidence of immune-mediated TEAEs.

2.4.4. Conclusions on clinical pharmacology

Systemic exposure of aflibercept was evaluated up to week 16 (4th injection) in a small subset of patients (n=8 for the Mynzepli product of interest) from the pivotal Phase III study AVT06-GL-C01. The serum concentrations were very low for both treatments and consistent with the range of Cmax stated in the SmPC of the reference medicinal product Eylea. Overall, these supportive and limited PK data do not indicate any major difference in systemic exposure between Mynzepli and the reference product Eylea, even though no formal PK comparison could be made and available data should only be considered for descriptive purpose.

The incidence of ADAs and nAbs was comparable between the two treatment groups.

The presented results support biosimilarity between test and reference product.

2.4.5. Clinical efficacy

The clinical development program was designed to demonstrate clinical similarity of Mynzepli to Eylea and composed of a single pivotal study conducted in patients with neovascular (wet) AMD (Study AVT06-GL-C01).

Clinical development consisting of one pivotal study was largely discussed in scientific advice and deemed acceptable to determine biosimilarity of the products in adult indications approved for EU Eylea.

Table 7: Clinical study AVT06-GL-C01

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
AVT06-GL-C01	Completed Start date: 28 Jun 2022 Total enrolment: 413 (AVT-06: 206, EU-Eylea: 207)	Phase III, randomized, double-masked, parallel-group, multicentre	2 mg/0.05 mL IVT injection of AVT-06 or EU- Eylea every 4 weeks for 3 consecutive monthly visits, followed by a injection every 8	Male and female Patients ≥ 50 years with neovascular (wet) AMD in the study eye

			weeks for 48 weeks total	

2.4.5.1. Dose-response studies

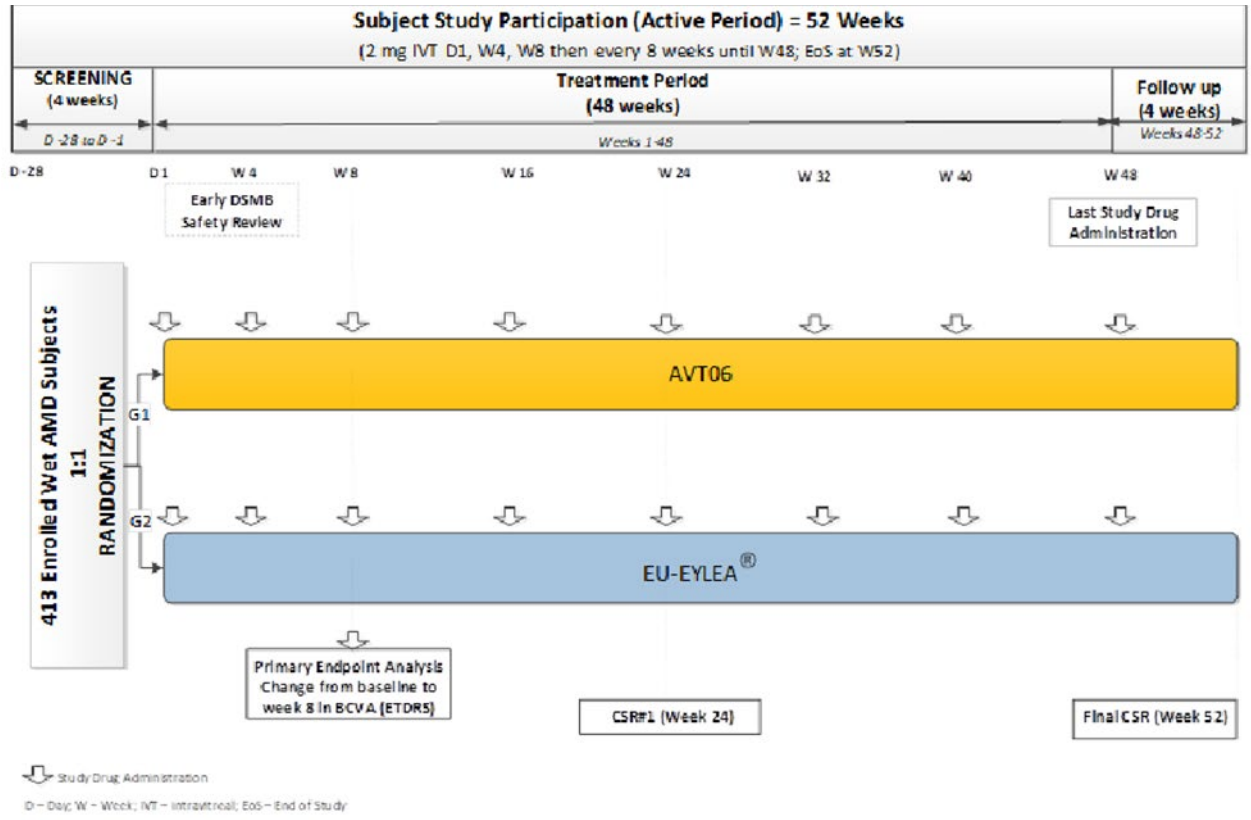
Not applicable

2.4.5.2. Main study

AVT06-GL-C01 - ALVOEYE

This was a multicentre, randomized, double-masked, parallel-group, therapeutic equivalence Phase 3 study designed to evaluate the efficacy, safety, and immunogenicity of Mynzepli compared with Eylea in participants with neovascular (wet) AMD. The study also evaluated the systemic PK of Mynzepli and Eylea in a subset of participants. The study consists of a screening period of up to 4 weeks, a treatment period of 48 weeks, and a follow-up period of 4 weeks until Week 52 (end of study). The total study duration is 56 weeks including screening period.

Figure 6: Study schema



Methods

Study Participants

Only 1 eye was designated as the study eye based on the inclusion and exclusion criteria. For subjects who met eligibility criteria in both eyes, the eye with the worse visual acuity was selected as the study eye. If both eyes had equal visual acuity, the eye with better visual prognosis (eg, clearer lens and ocular media and less amount of subfoveal scar or geographic atrophy) was selected as the study eye at the Investigator's discretion. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology, and subject's preference were considered by the Investigator in making the selection.

The main inclusion criteria were:

1. Male or female participants aged 50 years or more who had neovascular (wet) AMD in the study eye.

2. Subjects must have had active, treatment naïve, subfoveal CNV lesions secondary to neovascular (wet) AMD, including juxtafoveal lesions with foveal involvement (demonstrated by leakage on FA and/or intraretinal fluid or subretinal fluid on SD-OCT) in the study eye at screening.

3. Subjects with total lesion area ≤9.0 disc areas in size (including blood, scars [not involving the center of the fovea], and neovascularization) in the study eye at screening.

4. Subjects with active CNV area had occupied at least 50% of total lesion in the study eye.

5. Subjects with BCVA of 20/40 to 20/200 (between 73 and 34 letters inclusive), in the study eye as assessed by ETDRS letter score at screening and on Day 1 prior to randomization.

6. Presence of intra and/or subretinal fluid as identified in the center subfield by SD-OCT attributable to active CNV in the study eye at screening.

7. Subjects with central retinal thickness of ê300 µm in the study eye as determined by SD-OCT at screening.

Exclusion criteria were:

1. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.

2. History of retinal detachment in the study eye.

3. Presence of RPE tears involving the macula in the study eye.

4. History of any vitreous hemorrhage within 4 weeks before randomization in the study eye.

5. Prior vitrectomy or laser surgery of the macula (including photodynamic therapy or focal laser photocoagulation) in the study eye.

6. Uncontrolled ocular hypertension (defined as IOP ê25 mmHg despite treatment with anti-glaucoma medication) at screening and randomization visits in the study eye.

7. Any history of macular hole in the study eye.

8. Any concurrent macular abnormality other than wet AMD which could affect central vision or the efficacy of the study treatment in the study eye.

9. Aphakia or absence of the posterior capsule (unless it occurred as a result of a posterior capsulotomy with neodymium-doped yttrium aluminium garnet laser following cataract surgery with intraocular lens implantation) in the study eye.

10. Significant media opacities, including cataract or inadequate pupil dilatation, which might interfere with visual acuity or assessment of safety in the study eye.

11. Cataract surgery within 3 months from Day 1.

12. History of corneal transplant, corneal dystrophy, or corneal ectasia (such as either keratoconus or keratoglobus) in the study eye.

13. Subjects with previous ocular (intraocular and peribulbar) corticosteroids injection/implant within 1 year in the study eye prior to randomization.

14. Topical ocular corticosteroids for 30 or more consecutive days within 90 days prior to randomization in the study eye.

15. Previous therapeutic radiation in the region of the study eye.

16. Any prior ocular treatment, including surgery or another investigational product for neovascular AMD (including anti-VEGF therapy), in the study eye, except dietary supplements or vitamins.

17. Concurrent ocular condition which, in the opinion of the Investigator, could require medical or surgical intervention during the study period and/or confounded the interpretation of the study results.

18. History or clinical evidence of uveitis, diabetic retinopathy, diabetic macular edema, or any other vascular disease affecting the retina, other than neovascular AMD.

19. Active or suspected ocular or periocular infection, within 2 weeks before randomization.

20. Active scleritis or episcleritis or presence of scleromalacia.

21. Any ocular treatment, including surgery or another investigational product for neovascular AMD (including anti-VEGF treatment), in the fellow eye, within 6 months before randomization, except dietary supplements or vitamins.

22. Subjects with BCVA of 20/200 or less (34 letters or less) in the fellow eye as assessed by ETDRS letter score at screening and on Day 1 prior to randomization.

23. Subjects with any diagnosis and/or signs of neovascular AMD requiring intravitreal anti-VEGF in the fellow eye, or in the opinion of the Investigator, are expected to require such treatments before the evaluation of the primary efficacy endpoint (ie, Week 8) and completion of PK sampling (ie, Week 16) for the subjects in the PK substudy.

24. Any prior systemic treatment with anti-VEGF therapy.

25. History of hypersensitivity or anaphylaxis to study treatments (including any excipient), and/or history of hypersensitivity to fluorescein sodium for injection in angiography or to any other compound used for the study procedures.

26. Prior treatment with any investigational drugs within 30 days or 5 half-lives (whichever is longer) of the previous investigational treatment before initiation of the study treatment or concomitant enrolment in any other clinical study involving an investigational study treatment.

27. Uncontrolled diabetes mellitus with glycosylated hemoglobin (HbA1c) >8%.

28. Uncontrolled cardiovascular disease including hypertension, heart failure, or clinically significant electrocardiogram (ECG) abnormality, including subjects with QT interval corrected using Fridericia's formula (QTcF) >480 ms at screening, confirmed by repeat assessment. Uncontrolled hypertension is defined in Appendix 10 of the study protocol (Appendix 16.1.1).

29. Acute coronary event or stroke within 6 months before randomization.

30. Any condition that, in the Investigator´s opinion, might interfere with full participation in the study, including administration of the study treatment and attending required visits; might pose a significant risk to the subject, or interfered with interpretation of study data.

31. Malignancy diagnosed within 5 years, except treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, in situ prostate cancer, or in situ breast ductal carcinoma.

32. Subjects not suitable for participation, whatever the reason, as judged by the Investigator, including medical or psychiatric conditions, or subjects potentially at risk of noncompliance to study procedures.

33. Prior treatment with systemic steroids within 30 days of screening, with the exception of low stable doses of corticosteroids (defined as 10 mg or lower oral prednisolone or equivalent dose used for 90 days or more prior to screening). Nasal, dermal, and inhaled steroids were permitted.

34. Treatment with systemic medications known to be toxic to the lens, retina, or optic nerve including (but not limited to) deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, and ethambutol from the time of screening.

35. Any treatment that might affect study endpoint such as BCVA or CST (eg, Kallidinogenase or Jolethin for Japan subjects) within 5 × half-lives of the prohibited drug before randomization.

Treatments

In the study eye, subjects received 2 mg (0.05 mL) intravitreal injection of Mynzepli or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1, Week 4, and Week 8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24, 32, 40, and 48). Study treatment dose modification was not allowed in this study. The intravitreal injection was carried out under controlled aseptic conditions. Study treatment was administered after completing all study procedures except the postdose PK blood sampling and postdose IOP assessment. Following intravitreal injection, subjects were instructed to report any symptoms suggestive of endophthalmitis (eg, eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Table 8: Study Treatment Details

Study Treatment Name:	**AVT06**	**EU-Eylea**
Presentation	Vials	Prefilled syringe
Dosage formulation:	40 mg/mL	40 mg/mL
Unit Dose Strength(s)/dosage level(s):	2 mg (0.05 mL)	2 mg (0.05 mL)
Route of administration	Intravitreal	Intravitreal
Packaging and labeling	AVT06 was provided as single-dose vials. Each vial was labeled as required per country requirement. The ancillaries such as injection needles (BD precisionglide needle 30 G × ½ inch), hypodermic needle (18 G 1 × ½ inch), BD blunt filter needle (5 micron with blunt fill tip reference), and BD hypodermic 3-part Luer Lok syringes (1 mL) were supplied to the study centers.	Eylea was provided as single-dose prefilled syringes. Each prefilled syringe was labeled as required per country requirement. Injection needles (BD precisionglide needle 30 G × ½ inch) were supplied to the study centers.
Manufacturer	Alvotech Swiss AG	Bayer AG

Abbreviations: BD=Becton Dickinson.

Prior and concomitant therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject was receiving at the time of enrolment or received during the study were recorded in the eCRF.

Any concomitant procedures/surgeries that the subject was undergoing during the study were recorded in the eCRF along with name of the procedure, reason, and date of the procedure.

The COVID-19 vaccines under Emergency Use Authorization/conditional marketing authorization were regarded as commercialized vaccines, thus were allowed, except of those COVID-19 vaccines which are live or live-attenuated.

Other concomitant medications were considered on a case-by-case basis by the Investigator in consultation with the study medical monitor, if required.

Prohibited Medications/Therapy

Prohibited medications/therapy is listed in Table 9 below.

Table 9: Prohibited Medications

Prior vitrectomy or laser surgery of the macula (including photodynamic therapy or focal laser photocoagulation)	Study eye	Prior to screening to end of study/early termination visit.
Use of another investigational product for neovascular AMD	Study eye	Prior to screening to end of study/early termination visit.
Use of another investigational product for neovascular AMD	Fellow eye	Within 6 months before randomization to end of study/early termination visit.
Ocular or intravitreal anti-VEGF therapy	Study eye	Prior to screening to end of study/early termination visit.
Ocular or intravitreal anti-VEGF therapy	Fellow eye	Within 6 months before randomization to end of the study/early termination visit. During the study, if the subject develops wet AMD in the fellow eye and an acute treatment is needed: • The subject can only receive treatment with Eylea after Week 8 (primary efficacy endpoint assessment) and can remain in the study. If treatment is needed earlier, subjects can be discontinued as per Section 7.2. • Subjects in the PK analysis subgroup can only receive fellow eye treatment after the collection of serum concentration blood sample at Week 16. If treatment is needed between Week 8 and Week 16, subjects should be discontinued from the PK sub-study but can remain in the main study.
Prior systemic anti-VEGF therapy	Not applicable	Prior to screening and to end of study/early termination visit.
Systemic medications known to be toxic to the lens, retina, or optic nerve including (but not limited to) deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, and ethambutol	Not applicable	From screening to end of study/early termination visit.
Prior treatment with any investigational drugs within 5 half-lives of the previous investigational treatment before initiation of the study treatment and use of any other investigational products during the study are also prohibited. Investigator/study center staff can contact study Medical Monitor for guidance regarding concomitant medication use.		

Rescue medication for the study/fellow eye

No rescue medication was indicated in the protocol for the study eye.

However, during the course of the study, if the subject developed wet AMD in the fellow eye and an acute treatment was needed, the subject could only receive treatment with Eylea after Week 8 (primary efficacy endpoint assessment) and could remain in the study. If treatment was needed earlier, subjects were discontinued. Subjects in the PK analysis subgroup only received fellow eye treatment after the collection of serum concentration blood sample at Week 16. If treatment was needed between Week 8 and Week 16, subjects were discontinued from the PK substudy but remained in the main study. The fellow eye visit was not the part of study and was separated by at least 14 days from study eye treatment.

Objectives

Primary objective

Demonstrate the equivalent efficacy of Mynzepli to Eylea in subjects with neovascular (wet) AMD.

The primary endpoint was the mean change from baseline in BCVA using the ETDRS chart at Week 8. Equivalence between the main treatment groups was to be declared if the 95% (at EMA's request) and 90% (at FDA's request) CI of the difference is entirely contained within the pre-defined equivalence margin of [−3.5 letters, 3.5 letters].

Secondary objectives

The secondary objective of this study was to evaluate additional efficacy, pharmacokinetics (PK), usability, and overall safety including immunogenicity.

Outcomes/endpoints

Primary objective

Mean change from baseline in BCVA using the ETDRS chart at Week 8.

Secondary objectives

The following secondary efficacy endpoints were assessed at each applicable visit from baseline up to Week 52:

2. Mean change in BCVA using the ETDRS chart from baseline
3. Proportion of patients who gained ≥5, ≥10, and ≥15 letters in BCVA using the ETDRS chart
4. Proportion of patients who lost ≥5, ≥10, and ≥15 letters in BCVA using the ETDRS chart
5. Mean change in CST as determined by SD-OCT
6. Mean change of CNV lesion size using FA and Color FP

Sample size

Approximately 444 participants were planned to be randomly assigned to the study treatment to obtain approximately 398 evaluable participants for the analysis of primary endpoint of change from baseline to Week 8 in BCVA as assessed by ETDRS letter score. The study enrolment targeted approximately 30% of participants with light irides.

The sample size calculation assumed a true difference of 0.25 in the change from baseline to Week 8 in ETDRS letter score between Eylea and AVT06, standard deviation of 9.77, and a dropout rate of 10%. The equivalence test of means using 2 one-sided tests at a 2.5% significance level, corresponds to the two-sided 95% CI (as required by EMA and PMDA) and with 199 evaluable participants per group provides a power of 88.0% to reject the null hypothesis that difference in means between the 2 treatments is below -3.5 or above 3.5. This sample size provides a power of 93.8% at a 5% significance level, corresponding to two-sided 90% CI (as required by FDA), to reject the null hypothesis.

The proposed sample size of the Japanese subgroup targeted 14% of the overall sample size (i.e., approximately 62 Japanese participants).

Randomisation and blinding (masking)

Method of Assigning Subjects to Treatment Groups

All subjects were centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Subjects were randomly assigned in a 1:1 ratio to receive study treatment via

stratified randomization. The randomization was stratified by geographical origin (Europe, Americas, Japan, Other), baseline BCVA (≤53 letters versus ≥54 letters), and iris color (light irides versus non-light irides).

For each site participating in the PK substudy, once participants were screened into the main study, they were explained about PK substudy and were asked if they wanted to take part in the PK substudy. Subject participation in PK substudy was recorded in interactive response technology only after randomization for the main study. The IWRS was constructed to select consenting subjects to be included in the PK subpopulation in a masked fashion based on the treatment group to which they were randomized (approximately 20 subjects from each group).

Masking and Unmasking

Investigators, subjects, and the Sponsor or Sponsor's designee remained masked to each subject's assigned study treatment throughout the course of the study.

The Mynzepli and Eylea are not identical in physical appearance, as the first one is presented in vials (AVT06) the other one is presented in prefilled syringe (Eylea). This means that the treatments can be identified. In consequence, study treatment was only prepared and administered by delegated unmasked site staff. Neither the masked staff, nor the subject were present in the room during the IMP preparation by the unmasked study team.

In order to maintain the study masking, the authorized unmasked study center team was responsible for study treatment accountability, reconciliation, record maintenance, IMP temperature and preparation and administration of the study treatment (ie, receipt, reconciliation, preparation and administration, and final disposition records). No study center team member was assigned to perform both masked and unmasked tasks in the study. In addition, unmasked Sponsor or Sponsor's designee study team was responsible for the oversight of the study treatment handling activities (eg, drug accountability, reconciliation, disposition records).

In the event of a Quality Assurance audit, the auditor(s) were allowed access to unmasked study treatment records at the study center(s) to verify that randomization/dispensing had been done accurately.

In case of an emergency, the Investigator had the sole responsibility for determining if unmasking of a subject's treatment assignment was warranted. Subject safety was always the first consideration in making such a determination. If the Investigator decided that unmasking was warranted, he/she might, at his/her discretion, contacted the Sponsor to discuss the situation prior to unmasking a subject's treatment assignment, unless this could delay emergency treatment of the subject. In the event of subject's treatment assignment unmasked, the Sponsor or Sponsor's designee to be notified within 24 hours after breaking the masking. The date and reason that the masking was broken to be recorded in the source documentation and eCRF, as applicable.

Statistical methods

Statistical Hypotheses

Equivalence will be determined based on the change from baseline to Week 8 in BCVA as assessed by ETDRS letter score.

A meta-analysis of the VIEW 1, VIEW 2, HARRIER, and HAWK studies with aflibercept (Study NCT00509795, Study NCT00637377, Study NCT02434328, and Study NCT02307682, respectively) and the MARINA study with ranibizumab (Study NCT00056836) resulted in aflibercept versus sham

treatment difference of 8.27 letters (standard deviation 9.77) in the change in BCVA from baseline to Week 8 with 95% confidence interval (CI) (6.96, 9.59).

In accordance with the relevant FDA guideline on the selection of the noninferiority margin, an equivalence margin of [-3.5, 3.5] letters retain 50% of the original aflibercept treatment effect over sham. Based on the literature, a true difference of equal or less than 5 letters is not considered clinically meaningful.21, 22, 23, 24, 25, 26 Therefore, a margin of 3.5 letters is considered an adequate equivalence margin from a clinical and statistical perspective.

If the calculated two-sided 95% CI for the difference in means in change from baseline at Week 8 are completely contained within the equivalence margin [-3.5, 3.5], the null hypothesis $H0$: $\mu AVT06 - \mu EU{-}Eylea \leq -3.5$ or $\mu AVT06 - \mu EU{-}Eylea \geq 3.5$ will be rejected in favor of the alternative hypothesis HA: $|\mu AVT06 - \mu EU{-}Eylea| < 3.5$ where $\mu AVT06$ is the mean change from baseline to Week 8 for subjects randomized to receive Mynzepli and $\mu EU{-}Eylea$ is the mean change from baseline to Week 8 for subjects randomized to receive Eylea.

Analysis Sets

Agreement and authorization of subjects included/excluded from the primary endpoint analysis were conducted prior to Week 8 Database Freeze and unmasking of the study.

Table 10: Definition of analysis sets

Analysis Set	Description
Entered Analysis Set (ENR)	All subjects who signed the informed consent form.
Randomly Assigned to Study Treatment Analysis Set (RND)	All subjects in the ENR Set who were assigned to study treatment.
Full Analysis Set (FAS)	All subjects randomly assigned to study treatment and who received at least 1 dose of randomized study treatment in the study eye (AVT06 vial or Eylea Pre-filled syringe [PFS] only). Subjects were analyzed according to randomized treatment. All efficacy analyses were based on the FAS.
Safety Analysis Set (SAF)	All subjects randomly assigned to study treatment and who received at least 1 dose of study treatment. Subjects were analyzed according to the treatment they actually received.
Pharmacokinetic Analysis Set (PKS)	All subjects in the pharmacokinetic subset who received at least 1 dose of study treatment and had at least 1 pharmacokinetic result.

Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database freeze for the primary endpoint analysis at Week 8 and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Analysis for the primary endpoint will be performed as soon as all subjects have completed the Week 8 visit or withdrawn from the study prior to Week 8 and the database is freezed. Results of this analysis will be included in the CSR#1 and the Final CSR.

Analysis for CSR #1 will be undertaken after a database freeze, when all subjects complete Week 24 visit or have withdrawn from the study prior to Week 24.

Subsequent analyses will be performed when all subjects have completed the Week 52 visit or withdrawn from the study prior to Week 52. The Final CSR will include the primary endpoint analysis and the final analysis of the secondary efficacy endpoints up to and including Week 52, and analysis of all study data up to Week 52.

In order to preserve the double masking throughout the study duration and considering the planned primary study read out at Week 8 and CSR#1 at week 24, only prespecified individuals at the Sponsor or Sponsor's designee will become aware of the individual subject's treatment assignment at this point. The subjects and the masked Investigators as well as the masked team at the Sponsor or Sponsor's designee responsible for the study oversight/monitoring will remain masked to the individual subject's treatment assignment until the study completion. A dedicated unmasked team will be implemented within the Sponsor or Sponsor's designee prior to unmasking the Week 8 and Week 24 data. The unmasked team at the Sponsor or Sponsor's designee will not be involved in the direct conduct of the study nor study oversight after unmasking.

The roles and responsibilities of the unmasked team at Sponsor or Sponsor's designee will be detailed in the unmasking/masking study plan for the AVT06-GL-C01 study which will be approved prior to unmasking at Week 8.

All analyses, summaries, and listings will be performed using SAS® statistical software (version 9.4 or higher).

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

☐ Continuous variables: sample size [n], mean, standard deviation, median (q2), lower quartile (q1), upper quartile (q3), minimum [min], and maximum [max].

☐ Categorical variables: frequencies and percentages.

Efficacy Analyses

Table 11: Efficacy Analyses

Endpoint	Statistical Analysis Methods/Estimand Attributes
Primary: Change from baseline to Week 8 in BCVA as measured by ETDRS letter score	Endpoint: Change from baseline to Week 8 in BCVA as measured by ETDRS letter score. Population: Subjects with neovascular (wet) AMD, based on the FAS. Treatment: Randomized treatment groups, AVT06 and Eylea. In order to provide the most sensitive analysis set to detect potential differences between AVT06 compared with Eylea, the following ICEs that can lead to attenuation of differences are defined. Subjects' data at and after the occurrence of any of the following ICEs or additional protocol deviations will be excluded from the analysis. • Discontinuation from study treatment prior to Week 8. • Prohibited concomitant medications prior to Week 8 that impact the primary endpoint. • Received treatment from incorrect treatment group prior to Week 8. • Additional protocol deviations that impact the assessment of primary endpoint. Any additional criteria and/or protocol deviations that impact the primary endpoint will be defined in the SAP before database freeze for primary endpoint analysis at Week 8. Population Level Summary: The change from baseline to Week 8 in BCVA as measured by ETDRS letter score will be analyzed using a MMRM including the BCVA at baseline as covariate, geographical origin (Europe, Americas, Japan, Other), iris color (light irides/non-light irides), treatment, visit, and treatment-by-visit interaction as fixed effects. An unstructured covariance structure will be used to model the within-subject error and an adjustment to the degrees of freedom will be made using the Kenward-Roger's approximation. The LS mean estimates will be provided for each treatment group for each study visit time points along with their SE. The difference of LS means between the treatment groups and associated SE, two-sided 95% CI (as required by EMA) and two-sided 90% CI (as required by FDA) will be provided for Week 8. If these CIs are completely contained within the prespecified equivalence margin of letters of [-3.5 to 3.5], an efficacy equivalence can be demonstrated. **Sensitivity analyses:** Sensitivity analysis will be undertaken using the same analytical approach as for the main estimator based on the FAS without exclusion of any data for subjects with any of the ICEs specified for the main estimator. Details to sensitivity analysis will be provided in the SAP.

Secondary: Change from baseline in BCVA as measured by ETDRS letter score at Week 4, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52. Change from baseline in CST as assessed by SD-OCT at Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52. Change from baseline in CNV area as assessed by FA and color FP at Week 8, Week 24, and Week 52.	Endpoints: Change from baseline to Week 4, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52 in BCVA as measured by ETDRS letter score. Change from baseline in CST as assessed by SD-OCT at Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52. Change from baseline in CNV area as assessed by FA and color FP at Week 8, Week 24, and Week 52. Population: Subjects with neovascular (wet) AMD, based on the FAS. Treatment: Randomized treatment groups, AVT06 and Eylea. Population Level Summary: The change from baseline in BCVA as assessed by ETDRS letter score at Week 4, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52 will be obtained using the MMRM model used to analyze the primary estimand. At each time point the difference in the treatment group LS means and corresponding 95% CIs will be provided. For change from baseline in CST as assessed by SD-OCT at Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52 and change from baseline in CNV area as assessed by FA and color FP at Week 8, Week 24, and Week 52 a similar approach as for the primary efficacy variable will be used for the analysis. At each time point the difference in the treatment group LS means and corresponding 95% CIs will be provided. In the statistical analysis of secondary endpoints, 95% CIs will be interpreted descriptively (ie, no formal inferential statistical conclusions will be drawn).

Abbreviations: AMD = age-related macular degeneration, BCVA = Best-corrected Visual Acuity, CI = confidence interval, CNV = choroidal neovascularization, CST = central subfield thickness, EMA = European Medicines Agency, ETDRS = Early Treatment Diabetic Retinopathy Study, FA = fluorescein angiography, FAS = Full Analysis Set, FDA = Food and Drug Administration, FP = fundus photography, ICE = intercurrent event; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human; LS = least square, MMRM = mixed model for repeated measures, SAP = Statistical Analysis Plan, SD-OCT = spectral domain-optical coherence tomography, SE = standard error

The number and percentage of subjects who gain ê5, 10, 15 ETDRS letter score in BCVA from baseline to Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52, and the number and percentage of subjects who lose ê5, 10, 15 ETDRS letter score in BCVA from baseline to Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52 will be presented by treatment group. The difference in proportions and two-sided 95% CIs, will be presented for each gain/loss category for each analysis time point. In addition, the number and percentage of subjects with absence of intra-retinal and sub-retinal fluid from baseline to each Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 52 will be presented by treatment group. The difference in proportions and two-sided 95% CIs, will be presented for each analysis time point.

Primary efficacy endpoint is analysed by two ways: 1) "hypothetical strategy" analysis which is based on full analysis set (FAS) with exclusion of subject's data at and after occurrence of intercurrent event (ICE) and 2) "treatment policy strategy" analysis which is based on FAS without exclusion of any subject's data.

Justification of both strategies is based on statements in ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017), section A.3.4. Considerations for Constructing an estimand, as study is equivalence study.*Safety Analyses*

All safety analyses will be performed on the Safety Analysis Set (SAF).

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity after the first administration of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. For each study treatment, numbers of ocular TEAEs and incidence rates will be tabulated by preferred term and system organ class for the study eye and fellow eye separately.

Ocular, by study eye and fellow eye, and non-ocular TEAEs by maximum severity, TEAEs by relationship to study treatment, AESIs, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group.

All laboratory test results, vital signs measurements, ECG results, weight, and body mass index will be summarized for each treatment group using descriptive statistics at each visit and change from baseline. The incidence of treatment-emergent abnormal laboratory, vital sign, and ECG values will also be summarized using descriptive statistics.

Ophthalmic examination findings will be summarized using appropriate descriptive statistics.

Other Analyses

Pharmacokinetic Analyses

Serum concentrations of free and bound systemic aflibercept will be listed, summarized, and presented graphically by treatment and time point based on the Pharmacokinetic Analysis Set.

The Cmax and Tmax of free and bound aflibercept will be determined.

Concentrations that are below the lower limit of quantitation (LLOQ) will be set to 0.5 * LLOQ for the computation of descriptive statistics.

Immunogenicity Analyses

Immunogenicity (ADA and NAb) results will be listed by-subject and sampling time.

The number and proportion of subjects with positive and negative ADA and the number and proportion of subjects with positive and negative NAb will be summarized by treatment group and sampling time based on the SAF.

Missing Data

For the primary and secondary endpoint analysis, the missing data handling approach will be described in the SAP as needed.

Planned subgroup analyses

The main analysis for the primary efficacy endpoint will be repeated in the following subgroups using similar MMRM model for the primary analysis but excluding the respective subgroup as a fixed covariate:

x Geographical origin (Europe, Americas, Japan, Other)- MMRM model with BCVA at baseline as a continuous covariate, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects.

x Derived from Geographical origin & Race (Japanese, Non-Japanese)- MMRM model with BCVA at baseline as a continuous covariate, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects.

x Baseline BCVA (≤53 letters vs. ≥ 54 letters)- MMRM model with, geographical origin, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects.

x Iris color (light irides/non-light irides)- MMRM model with BCVA at baseline as a continuous covariate, geographical origin, treatment, visit, and treatment-by-visit interaction as fixed effects.

x Baseline CST (< 400.0 and ≥ 400.0 µm)- MMRM model with BCVA at baseline as a continuous covariate, geographical origin, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects.

x ADA (positive / negative) – (note: positive if any at Baseline, Week 4, Week 8 is positive, negative otherwise)- MMRM model with BCVA at baseline as a continuous covariate, geographical origin, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects.

x NAb (positive / negative) – (note: positive if any at Baseline, Week 4, Week 8 is positive, negative otherwise)- MMRM model with BCVA at baseline as a continuous covariate, geographical origin, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects.

The statistical analysis results of subgroups will be interpreted descriptively (i.e., no formal inferential statistical conclusions will be drawn).

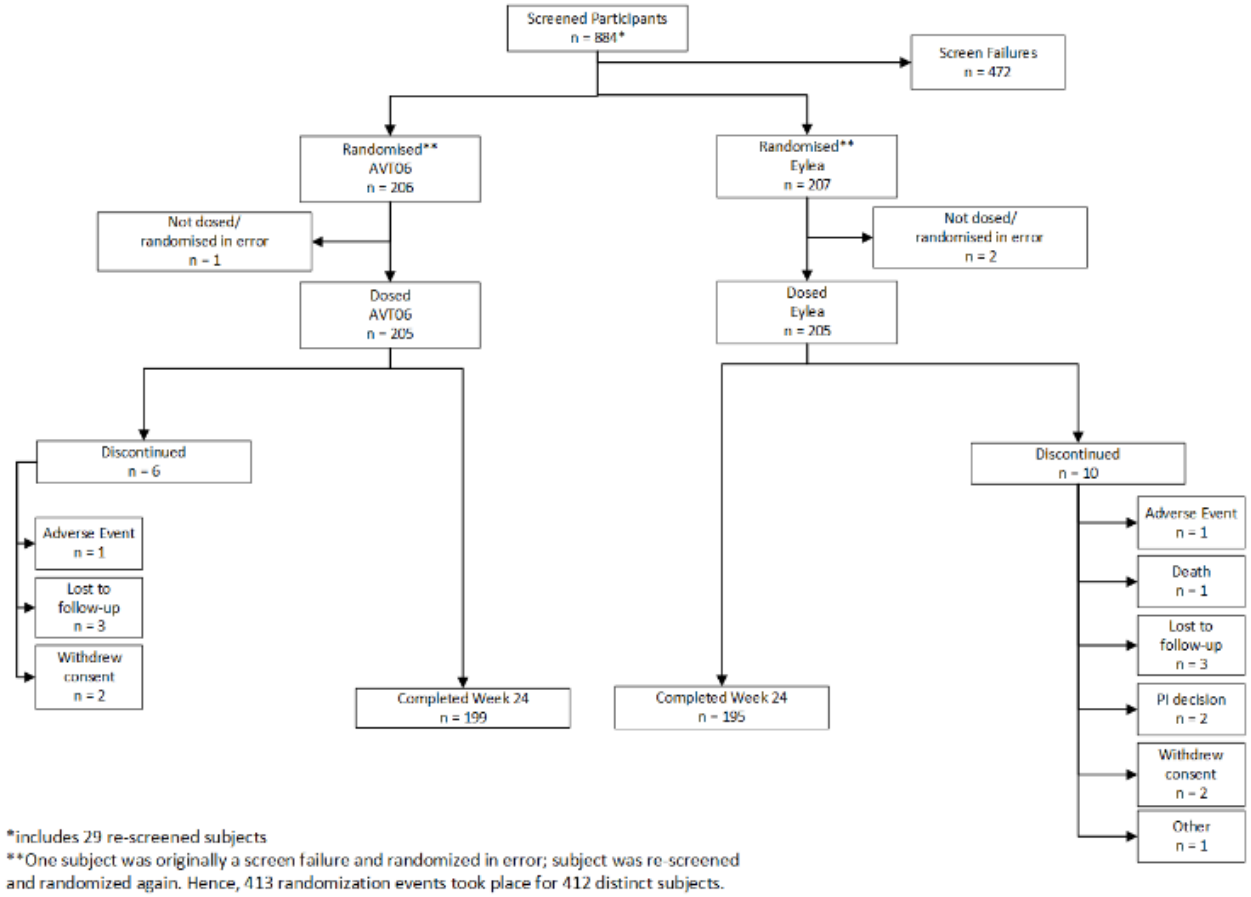
Error probabilities, adjustment for multiplicity and interim analyses

No interim analysis was planned for this study.

Results

Participant flow

Figure 7: Participant flow up to Week 24



*includes 29 re-screened subjects
**One subject was originally a screen failure and randomized in error; subject was re-screened and randomized again. Hence, 413 randomization events took place for 412 distinct subjects.

A total of 855 subjects were screened, of which 413 subjects were randomized to the study treatment (205 subjects received AVT06, and 205 received EU-Eylea) and 472 subjects had screened failure. Among the 413 subjects, 394 subjects completed the study treatment up to Week 24. Moreover, the applicant provided justification for the reasons behind screen failures.

Recruitment

First Subject First Visit: 29 June 2022

Last Subject Last Visit: The study was ongoing at the time of MAA submission

Database lock date (Week 24 primary endpoint analysis): 08 March 2024

Conduct of the study

Table 12: AVT06-GL-C01 Protocol amendments

Number (date of internal approval)	Key details of amendment (Section of this report affected)
Amendments Made Before the Start of Subject Recruitment	
Global Amendment	
Protocol Version 2.0 dated 21 December 2021	• Secondary endpoints were added to implement regulatory authority advice.
	• Secondary immunogenicity endpoint was updated to implement regulatory authority advice and for consistency with PK sampling schedule.
	• Additional time points were introduced under secondary PK endpoints to allow robust evaluation of C_{max} after repeat dosing at Week 8 (postdose) and Week 16 of free and bound aflibercept as per regulatory authority recommendation.
	• Number of subjects was modified to implement regulatory authority advice to include at least 30% of subjects with light irides.
	• Treatment groups and duration was updated to implement regulatory authority advice.
	• Statistical methods, information regarding $C_{trough,ss}$ was removed as $C_{trough,ss}$ was no longer required per study objectives.
	• New exclusion criterion (criterion #11) "Cataract surgery within 3 months from Day 1" was added for clarification.
	• Information under measures to minimize bias section was updated considering regulatory authority advice to include geographical origin (instead of location) as stratification factor as well as iris color for robust analyses of the primary endpoint.
	• Approximate blood volume was updated which was required for the study assessments in alignment with the Section 1.3: Schedule of Activities.
	• Best-Corrected Visual Acuity section was updated to clarify acceptable ETDRS charts for use in the study.
	• Statistical Hypotheses was updated to further support the robustness of the proposed equivalence margin.
	• Efficacy analysis was modified to be in accordance with ICH E9 (R1) with regards to intercurrent events definition per estimand concept approach and to include the statistical analyses for the new secondary endpoints.
	• Missing data was updated to missing data handling approach for primary and secondary endpoints for clarity.

Country-specific Amendment	
Protocol Version 2.1 – The Czech Republic dated 23 May 2022	• Schedule of activities were updated to implement the regulatory authority (The Czech Republic Competent Authority) advice.
	• Inclusion criteria, dosing instructions, and temporary discontinuation of study treatment were updated to implement regulatory authority advice.
Amendments Made After the Start of Subject Recruitment	
Global Amendments	
Protocol Version 3.0 dated 21 October 2022	• The primary endpoint was updated to be aligned with the estimand concept approach as per ICH E9 (R1) addendum on estimands.
	• Schedule of activities was updated with respect to study eye color to implement regulatory authority request. This section was also updated for clarity on protocol requirements for the Czech Republic sites. Additionally, in this section, ophthalmological assessments on D2, D3, W8 D2 and W8 D3 removed for PK substudy simplification.
	• Exclusion criteria #33 and #34 were added in alignment with Appendix 5 prohibited medications/therapy and exclusion criterion #35 was added for clarification under exclusion criteria.
	• Study assessments and procedures was updated to clarify eligibility procedure for image reading. In this section, blood volume was also updated in alignment with final calculations from central laboratory on the blood volumes required.
	• Fluorescein angiography and color fundus photography was updated as per DSMB request to confirm diagnose of retinal vasculitis of either occlusive or non-occlusive.
	• Pharmacokinetics was updated to allow sensitivity analyses in case of differences in drug protein content between AVT06 and EU-Eylea to be in line with regulatory authority requirements.
	• Efficacy analyses was updated to be aligned with the estimand concept approach as per ICH E9 (R1) addendum on estimands.
	• Appendices 8, 9 and 10 were added to protocol from procedure manual. Appendix 11 intraocular inflammation classification and grading scales was added to collect additional information regarding intraocular inflammation events.
Protocol Version 4.0 dated 09 August 2023	• Criteria for evaluable subjects was updated to align with ICH E9. Other changes for better clarity in alignment with other protocol sections were also done.
	• Table 4 Schedule of Activities - Pharmacokinetics Substudy was updated for better clarity for schedule time of PK sample.
	• Introduction and Background sections were updated as per IB Edition 5 and most current SmPC for EU Eylea.
	• Inclusion criteria with respect to age was modified to implement country specific (the Czech Republic) approved change into global amendment.
	• Statistical analysis was updated in alignment of the modified schema and the current plan for preparation of CSR at Week 24 instead of Week 16 for global regulatory submission. Also, clarity added for primary endpoint analysis.

Abbreviations: CSR=clinical study report, C_{max}=maximum observed concentration, $C_{trough,ss}$=trough serum concentration, measured concentration at the end of a dosing interval at steady state, D=day, DSMB= Data Safety Monitoring Board, ETDRS=Early Treatment Diabetic Retinopathy Study, EU=Europe, IB=Investigator's Brochure, ICH=International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, PK=pharmacokinetics, R1=revision 1, SmPC= Summary of Product Characteristics; W=week.

Protocol deviations

A total of 246 (60%) subjects (Mynzepli: 117; Eylea: 129) had any protocol deviations. Overall, 7 (1.7%) subjects had any critical protocol deviations, 116 (28.3%) had any major protocol deviations, and 208 (50.7%) had any minor protocol deviations. It is to be noted that some subjects had more than 1 category of protocol deviations (ie, the subject had either minor and major, minor and critical, major and critical, or critical, major, and minor protocol deviations). The proportion of subjects with critical/major/minor protocol deviations were comparable between the treatment groups.

Table 13: Summary of Protocol Deviations up to Week 24 (FAS)

Description	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
Subjects with any protocol deviation	117 (57.1)	129 (62.9)	246 (60.0)
Subjects with any critical protocol deviation	3 (1.5)	4 (2.0)	7 (1.7)
Subjects with any major protocol deviation	54 (26.3)	62 (30.2)	116 (28.3)
Subjects with any minor protocol deviation	97(47.3)	111 (54.1)	208 (50.7)

Abbreviations: FAS=Full Analysis Set, n=Number of subjects.

Percentages were based on the total number of subjects in the FAS for each treatment group and total column unless otherwise stated.

Data cut-off=16 April 2024. Only data up to the Week 24 visit is presented.

Important Protocol Deviations

Important protocol deviations are a subset of protocol deviations that might significantly impact the completeness, accuracy and/or reliability of study data or that might significantly affect the subject's rights, safety, or well-being. The important protocol deviations up to Week 24 in the FAS are summarized in table below.

Table 14: Summary of Important Protocol Deviations up to Week 24 (FAS)

Description	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
Subjects with at least one important protocol deviation	38 (18.5)	44 (21.5)	82 (20.0)
Concomitant medication	1 (0.5)	0	1 (0.2)
Efficacy	0	1 (0.5)	1 (0.2)
Exclusion criteria	1 (0.5)	2 (1.0)	3 (0.7)
Inclusion criteria	1 (0.5)	0	1 (0.2)
Informed consent and process	5 (2.4)	5 (2.4)	10 (2.4)
IP administration	3 (1.5)	4 (2.0)	7 (1.7)
Laboratory assessment	7 (3.4)	9 (4.4)	16 (3.9)
Patient reported outcomes	0	1 (0.5)	1 (0.2)
Randomization	13 (6.3)	12 (5.9)	25 (6.1)
Safety	0	2 (1.0)	2 (0.5)
Study procedures	15 (7.3)	16 (7.8)	31 (7.6)
Subject IP compliance	1 (0.5)	1 (0.5)	2 (0.5)
Visit schedule	1 (0.5)	0	1 (0.2)
Subjects with at least one other protocol deviation	104 (50.7)	117 (57.1)	221 (53.9)
Administrative	0	1 (0.5)	1 (0.2)
Informed consent and process	3 (1.5)	1 (0.5)	4 (1.0)
IP administration	3 (1.5)	5 (2.4)	8 (2.0)
Laboratory assessment	48 (23.4)	50 (24.4)	98 (23.9)
Randomization	6 (2.9)	7 (3.4)	13 (3.2)
Safety	3 (1.5)	6 (2.9)	9 (2.2)
Study procedures	60 (29.3)	72 (35.1)	132 (32.2)
Visit schedule	32 (15.6)	30 (14.6)	62 (15.1)

Abbreviations: FAS=Full Analysis Set, IP=investigational product, n=Number of subjects.

Percentages were based on the total number of subjects in the FAS for each treatment group and total column unless otherwise stated.

Important protocol deviations are a subset of protocol deviations that might significantly impact the completeness, accuracy and/or reliability of study data or that might significantly affect the subject's rights, safety, or well-being.

Data cut-off=16 April 2024. Only data up to the Week 24 visit is presented.

The intercurrent events (ICEs) or protocol deviations leading to exclusion of data from the primary endpoint (change from baseline to Week 8 in BCVA as measured by EDTRS letter score) in the FAS is summarized in table 15 below. Overall, 4 subjects (Mynzepli: 1; Eylea: 3) had ICEs and protocol deviations that led to exclusion of data from the analysis for primary endpoint.

Table 15: Summary of ICEs and Protocol Deviations Leading to Exclusion of Data from Primary Endpoint (FAS)

Description	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
Subjects with any ICE or protocol deviation leading to exclusion of data from primary endpoint	1 (0.5)	3 (1.5)	4 (1.0)
Discontinuation from study treatment prior to Week 8	0	2 (1.0)	2 (0.5)
Prohibited concomitant medications prior to Week 8 that impact the primary endpoint	0	0	0
Received treatment from incorrect treatment group prior to Week 8	0	0	0
Additional protocol deviations that impact the assessment of primary endpoint			
Violation of inclusion/exclusion criteria	1 (0.5)	1 (0.5)	2 (0.5)
Subjects missing BCVA assessments up to Week 8			
Week 4	0	1 (0.5)	1 (0.2)
Week 8	1 (0.5)	3 (1.5)	4 (1.0)

Abbreviations: BCVA=Best-corrected Visual Acuity, FAS=Full Analysis Set, ICE=intercurrent event, n=Number of subjects.

Percentages were based on the total number of subjects in the FAS for each treatment group and total column unless otherwise stated.

Following are the details on exclusion of subject's data from the primary endpoint analysis:

Subject 110406, excluded from the primary endpoint analysis due to the data being impacted by the occurrence of ICEs (Week 4 and Week 8 assessment not performed).

Subject 180203, Week 8 assessment was excluded from the primary endpoint analysis due to the data being impacted by the occurrence of ICEs (Week 8 visit not performed).

Subject 110501 and 270204, excluded from the primary endpoint analysis due to the data being impacted by the occurrence of ICEs (violated the inclusion criteria).

Subject 110911 and 170522, Week 8 visit was not performed, therefore only baseline and Week 4 assessment was used in the primary endpoint analysis. The Week 8 visit was not impacted by the occurrence of ICEs.

Data cut-off=16 April 2024.

Baseline data

Demographic Characteristics

Table 16: Subject Demographics and Other Baseline Characteristics (FAS)

Description	Statistic	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
Age (years)	n	205	205	410
	Mean (SD)	73.7 (9.11)	74.3 (8.04)	74.0 (8.58)
	Median	74.0	75.0	74.0
	Min, Max	51, 96	51, 91	51, 96
Sex				
Male	n (%)	102 (49.8)	89 (43.4)	191 (46.6)
Female	n (%)	103 (50.2)	116 (56.6)	219 (53.4)
Childbearing potential [a]				
Yes	n (%)	0	0	0
No	n (%)	103 (100.0)	116 (100.0)	219 (100.0)
Ethnicity				
Hispanic or Latino	n (%)	36 (17.6)	39 (19.0)	75 (18.3)
Not Hispanic or Latino	n (%)	166 (81.0)	160 (78.0)	326 (79.5)
Not reported	n (%)	3 (1.5)	6 (2.9)	9 (2.2)
Unknown	n (%)	0	0	0
Race[1]				
American Indian or Alaska Native	n (%)	0	0	0
Asian	n (%)	34 (16.6)	33 (16.1)	67 (16.3)
Black or African American	n (%)	1 (0.5)	1 (0.5)	2 (0.5)
Native Hawaiian or other Pacific Islanders	n (%)	0	0	0
White	n (%)	154 (75.1)	158 (77.1)	312 (76.1)
Japanese	n (%)	14 (6.8)	13 (6.3)	27 (6.6)
Multiple	n (%)	1 (0.5)	0	1 (0.2)
Not Reported	n (%)	1 (0.5)	0	1 (0.2)
Unknown	n (%)	0	0	0
Japanese Subgroup				
Japanese	n (%)	15 (7.3)	13 (6.3)	28 (6.8)
Non-Japanese	n (%)	190 (92.7)	192 (93.7)	382 (93.2)
Height (cm)	n	205	203	408
	Mean (SD)	164.87 (10.033)	163.97 (9.202)	164.42 (9.627)
	Median	164.00	164.00	164.00
	Min, Max	125.5, 190.0	142.0, 194.0	125.5, 194.0
Weight (kg)	n	205	203	408
	Mean (SD)	74.46 (15.375)	73.69 (14.904)	74.08 (15.129)
	Median	72.00	73.40	73.00
	Min. Max	42.0. 126.0	41.6. 120.0	41.6. 126.0
BMI (kg/m^2)	n	205	203	408
	Mean (SD)	27.32 (4.595)	27.34 (4.670)	27.33 (4.627)
	Median	26.70	27.00	26.80
	Min, Max	16.9, 41.3	14.5, 41.6	14.5, 41.6
Geographical origin (IWRS)				
Europe	n (%)	117 (57.1)	117 (57.1)	234 (57.1)
Americas	n (%)	36 (17.6)	37 (18.0)	73 (17.8)
Japan	n (%)	15 (7.3)	13 (6.3)	28 (6.8)
Other	n (%)	37 (18.0)	38 (18.5)	75 (18.3)
Iris color (IWRS)				
Light irides	n (%)	96 (46.8)	96 (46.8)	192 (46.8)
Non-light irides	n (%)	109 (53.2)	109 (53.2)	218 (53.2)
Primary diagnosis of neovascular AMD				
Yes	n (%)	205 (100.0)	205 (100.0)	410 (100.0)
No	n (%)	0	0	0
Time since diagnosis of neovascular AMD (Days)	n	156	157	313
	Mean (SD)	42.9 (157.98)	46.2 (138.16)	44.5 (148.14)
	Median	21.0	22.0	21.0
	Min, Max	6, 1965	6, 1581	6, 1965
Neovascular AMD				
Unilateral	n (%)	176 (85.9)	176 (85.9)	352 (85.9)

Bilateral	n (%)	29 (14.1)	29 (14.1)	58 (14.1)
Baseline BCVA Score (IWRS)	n	205	205	410
	Mean (SD)	55.8 (11.72)	54.2 (12.38)	55.0 (12.07)
	Median	57.0	55.0	56.0
	Min, Max	34, 73	24, 73	24, 73
Baseline BCVA Score				
≤53	n (%)	97 (47.3)	99 (48.3)	196 (47.8)
≥54	n (%)	108 (52.7)	106 (51.7)	214 (52.2)
Baseline CST (µm)	n	205	205	410
	Mean (SD)	430.9 (117.46)	436.2 (128.12)	433.6 (122.79)
	Median	398.0	401.0	399.5
	Min, Max	189, 873	262, 970	189, 970
Baseline CST (µm)				
<400 µm	n (%)	104 (50.7)	101 (49.3)	205 (50.0)
≥400 µm	n (%)	101 (49.3)	104 (50.7)	205 (50.0)
Lesion Type				
Predominantly classic	n (%)	67 (32.7)	45 (22.0)	112 (27.3)
Minimally classes	n (%)	36 (17.6)	52 (25.4)	88 (21.5)
Pure occult	n (%)	98 (47.8)	106 (51.7)	204 (49.8)
PCV	n (%)	2 (1.0)	1 (0.5)	3 (0.7)
RAP	n (%)	2 (1.0)	1 (0.5)	3 (0.7)
Foveal Involvement				
Subfoveal	n (%)	205 (100.0)	205 (100.0)	410 (100.0)
Extrafoveal	n (%)	0	0	0
Undeterminable	n (%)	0	0	0
Fluid Status				
Intraretinal fluid				
Definite	n (%)	142 (69.3)	132 (64.4)	274 (66.8)
Questionable	n (%)	18 (8.8)	18 (8.8)	36 (8.8)
Absent	n (%)	45 (22.0)	55 (26.8)	100 (24.4)
Subretinal fluid				
Definite	n (%)	186 (90.7)	186 (90.7)	372 (90.7)
Questionable	n (%)	6 (2.9)	7 (3.4)	13 (3.2)
Absent	n (%)	13 (6.3)	12 (5.9)	25 (6.1)
ADA				
Positive	n (%)	10 (4.9)	14 (6.8)	24 (5.9)
Negative	n (%)	189 (92.2)	186 (90.7)	375 (91.5)
Not available	n (%)	6 (2.9)	5 (2.4)	11 (2.7)
Nab				
Positive	n (%)	0	2 (1.0)	2 (0.5)
Negative	n (%)	10 (4.9)	12 (5.9)	22 (5.4)
Not available	n (%)	195 (95.1)	191 (93.2)	386 (94.1)

Abbreviations: ADA=anti-drug antibodies, AMD=age-related macular degeneration, BCVA=Best-corrected Visual Acuity, BMI=body mass index, CST=central subfield thickness, FAS= Full Analysis Set, IWRS=Interactive Web Response System, n=Number of subjects, NAb=neutralizing ADA, PCV=Polypoidal Choroidal Vasculopathy, RAP=Retinal Angiomatous Proliferation, SD=standard deviation.

[1]Subject 190503 reported multiple races ('Asian' and 'Japanese'). They contribute to the 'Multiple' rows only.

Japanese subgroup was derived from geographical origin and race (Japanese, Non-Japanese). Subject 190503 was included in the 'Japanese' category.

Body Mass Index (BMI) (kg/m^2)=weight (kg)/height (m)^2.

Age (years) at date of signed informed consent.

Percentages were based on the total number of subjects in the Full Analysis Set per treatment group.

[a] Percentages were calculated out of the number of female subjects per treatment group.

Data cut-off=16 April 2024.

Overall, baseline characteristics are deemed similar between Mynzepli and EU-Eylea groups. Baseline characteristics are deemed similar between Mynzepli and EU-Eylea groups for CNV lesion size (mm2) and IOP (mmHg).

Medical History

Ocular Medical History

Table 17: Summary of Ocular Medical History by Study Eye (SAF)

System Organ Class Preferred Term	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
Subjects with any Ocular Medical History - Study Eye	205 (100.0)	205 (100.0)	410 (100.0)
Eye disorders	205 (100.0)	205 (100.0)	410 (100.0)
Neovascular age-related macular degeneration	205 (100.0)	205 (100.0)	410 (100.0)
Cataract	90 (43.9)	103 (50.2)	193 (47.1)
Pseudophakia	20 (9.8)	26 (12.7)	46 (11.2)
Dry age-related macular degeneration	19 (9.3)	20 (9.8)	39 (9.5)
Open angle glaucoma	8 (3.9)	14 (6.8)	22 (5.4)
Cataract nuclear	16 (7.8)	3 (1.5)	19 (4.6)
Myopia	9 (4.4)	8 (3.9)	17 (4.1)
Hypermetropia	6 (2.9)	6 (2.9)	12 (2.9)
Posterior capsule opacification	5 (2.4)	6 (2.9)	11 (2.7)
Astigmatism	4 (2.0)	6 (2.9)	10 (2.4)
Glaucoma	4 (2.0)	6 (2.9)	10 (2.4)
Vitreous floaters	4 (2.0)	6 (2.9)	10 (2.4)
Presbyopia	5 (2.4)	4 (2.0)	9 (2.2)
Retinal degeneration	3 (1.5)	4 (2.0)	7 (1.7)
Dry eye	3 (1.5)	3 (1.5)	6 (1.5)
Arteriosclerotic retinopathy	3 (1.5)	1 (0.5)	4 (1.0)
Vitreous degeneration	1 (0.5)	3 (1.5)	4 (1.0)
Cataract cortical	1 (0.5)	2 (1.0)	3 (0.7)
Pterygium	3 (1.5)	0	3 (0.7)
Vitreous detachment	1 (0.5)	2 (1.0)	3 (0.7)
Blepharochalasis	2 (1.0)	0	2 (0.5)
Epiretinal membrane	1 (0.5)	1 (0.5)	2 (0.5)
Exfoliation syndrome	2 (1.0)	0	2 (0.5)
Eyelid ptosis	2 (1.0)	0	2 (0.5)
Vitreous opacities	0	2 (1.0)	2 (0.5)
Age-related macular degeneration	1 (0.5)	0	1 (0.2)
Arcus lipoides	1 (0.5)	0	1 (0.2)
Asthenopia	0	1 (0.5)	1 (0.2)
Borderline glaucoma	1 (0.5)	0	1 (0.2)
Cataract subcapsular	0	1 (0.5)	1 (0.2)
Dacryostenosis acquired	0	1 (0.5)	1 (0.2)
Eye discharge	1 (0.5)	0	1 (0.2)
Hyalosis asteroid	1 (0.5)	0	1 (0.2)
Lacrimation increased	1 (0.5)	0	1 (0.2)
Lenticular opacities	1 (0.5)	0	1 (0.2)
Retinal haemorrhage	0	1 (0.5)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	3 (1.5)	4 (1.0)
Benign neoplasm of eyelid	1 (0.5)	1 (0.5)	2 (0.5)
Blepharal papilloma	0	1 (0.5)	1 (0.2)
Eye naevus	0	1 (0.5)	1 (0.2)
Surgical and medical procedures	2 (1.0)	1 (0.5)	3 (0.7)
Intraocular lens implant	1 (0.5)	1 (0.5)	2 (0.5)
Laser therapy	1 (0.5)	0	1 (0.2)
Injury, poisoning and procedural complications	1 (0.5)	1 (0.5)	2 (0.5)
Injury corneal	0	1 (0.5)	1 (0.2)
Injury of conjunctiva	0	1 (0.5)	1 (0.2)
Pseudophakic bullous keratopathy	1 (0.5)	0	1 (0.2)
Congenital, familial and genetic disorders	0	1 (0.5)	1 (0.2)
Retinal anomaly congenital	0	1 (0.5)	1 (0.2)
Immune system disorders	0	1 (0.5)	1 (0.2)
Drug hypersensitivity	0	1 (0.5)	1 (0.2)
Infections and infestations	1 (0.5)	0	1 (0.2)
Ophthalmic herpes zoster	1 (0.5)	0	1 (0.2)
Product issues	0	1 (0.5)	1 (0.2)
Device dislocation	0	1 (0.5)	1 (0.2)

Data cut-off = 16APR2024.
Abbreviations: n = Number of subjects.
Subjects with more than one event within a SOC or PT are counted only once for that SOC or PT.
Medical and ophthalmic history are coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 26.0.
Medical history conditions are defined as those conditions which started prior to or at screening.
Percentages are calculated out of the number of subjects included in the safety analysis set per treatment group.

Non-ocular Medical History

A total of 339 (82.7%) subjects (Mynzepli: 166 [81%]; Eylea: 173 [84.4%]) had the history of non-ocular disorders.

More than 25% of the subjects in either of the treatment groups had the history of following non-ocular disorders (by system organ class [SOC]): vascular disorders (Mynzepli: 63.9%; Eylea: 62.4%),

metabolism and nutrition disorders (Mynzepli: 42.9%; Eylea: 43.9%), and cardiac disorders (Eylea: 25.9%).

More than 10% of the subjects in either of the treatment groups had the history of following non-ocular disorders (by PT): hypertension (Mynzepli: 53.7%; Eylea: 50.7%), hypercholesterolemia (Mynzepli: 16.6%; Eylea: 17.1%), osteoarthritis (Eylea: 12.7%), type 2 diabetes mellitus (Mynzepli: 11.2%), dyslipidemia (Mynzepli: 10.7%), hypothyroidism (Eylea: 10.2%), and menopause (Eylea: 10.7%).

Prior and Concomitant Medications

Prior and Concomitant Ocular Medications

All 410 subjects were reported with at least 1 prior or concomitant medications up to Week 24.

More than 25% of the subjects in either of the treatment groups reported the use of following prior or concomitant medications (by ATC Level 2): opthalmologicals (Mynzepli: 100%; Eylea: 100%), diagnostic agents (Mynzepli: 97.1%; Eylea: 96.1%), agents acting on the renin-angiotensin system (Mynzepli: 48.8%; Eylea: 45.4%), lipid modifying agents (Mynzepli: 36.1%; Eylea: 33.7%), beta blocking agents (Mynzepli: 28.3%; Eylea: 33.7%), and antithrombotic agents (Mynzepli: 21%; Eylea: 25.4%).

More than 25% of the subjects in either of the treatment groups reported the use of following prior or concomitant medications (by preferred drug name): fluorescein as a diagnostic agent (Mynzepli: 97.1%; Eylea: 96.1%), povidone-iodine (Mynzepli: 91.7%; Eylea: 90.7%), tropicamide (Mynzepli: 72.2%; Eylea: 68.8%), proxymetacaine (Mynzepli: 68.3%; Eylea: 71.7%), moxifloxacin (Mynzepli: 32.2%; Eylea: 35.6%), and fluorescein (Mynzepli: 31.2%; Eylea: 30.7%).

Prior and Concomitant Non-ocular Medications

A total of 337 (82.2%) subjects (Mynzepli: 170 [82.9%]; Eylea: 167 [81.5%]) were reported with at least 1 prior or concomitant non-ocular medications up to Week 24.

More than 10% of the subjects in either of the treatment groups were reported with the use of following prior or concomitant non-ocular medications (by preferred drug name): rosuvastatin (Mynzepli: 14.1%; Eylea: 14.6%), atorvastatin (Mynzepli: 14.6%; Eylea: 10.7%), bisoprolol (Mynzepli: 12.2%; Eylea: 10.7%), metoprolol (Mynzepli: 4.9%; Eylea: 10.2%), acetylsalicylic acid (Mynzepli: 13.7%; Eylea: 13.2%), metformin (Mynzepli: 10.2%; Eylea: 9.8%), amlodipine (Mynzepli: 8.3%; Eylea: 14.1%), COVID-19 vaccine (Mynzepli: 11.2%; Eylea: 14.6%), and levothyroxine (Mynzepli: 10.7%; Eylea: 10.2%).

Prior and Concomitant Procedures

Prior and concomitant procedures are defined as those procedures that are performed within the 30 days prior starting the treatment.

Prior and Concomitant Procedures in the Study Eye

Overall, 110 (26.8%) subjects (Mynzepli: 55 [26.8%]; Eylea: 55 [26.8%]) were reported with at least 1 prior or concomitant procedures in the study eye up to Week 24. More than 1% of the subjects in either of the treatment groups were reported with the following prior or concomitant procedures (by PT) in the study eye: cataract operation (Mynzepli: 24.9%; Eylea: 24.9%) and intraocular lens implant (Mynzepli: 1%; Eylea: 2.4%).

One (0.5%) subject (#120101) in the Eylea group underwent paracentesis eye (SOC: ocular paracentesis) to lower IOP in the study eye on Day 57.

Prior and Concomitant Ocular Procedures

Overall, 117 (28.5%) subjects (Mynzepli: 61 [29.8%]; Eylea: 56 [27.3%]) were reported with at least 1 prior ocular surgical and medical procedures. More than 1% of the subjects in either of the treatment groups were reported with the following prior ocular procedures (by PT): cataract operation (Mynzepli: 26.3%; Eylea: 26.3%), intraocular lens implant (Mynzepli: 1%; Eylea: 2.9%), and posterior lens capsulotomy (Mynzepli: 1.5%; Eylea: 1%).

Overall, 10 (2.4%) subjects (Mynzepli: 2 [1%]; Eylea: 8 [3.9%]) were reported with at least 1 concomitant ocular procedure up to Week 24; 8 subjects (Mynzepli: 1; Eylea: 7) had surgical and medical procedures, and 2 subjects (Mynzepli: 1; Eylea: 1) had investigations. More than 1% of the subjects in either of the treatment groups had cataract operation (Eylea: 2.4%) during first 24 weeks of the treatment.

Prior and Concomitant Non-Ocular Procedures

Overall, 4 (1%) subjects (Mynzepli: 2 [1%]; Eylea: 2 [1%]) were reported with at least 1 prior non-ocular surgery or procedures; 1 subject each in Mynzepli group had aspiration joint and ultrasound abdomen, and 1 subject each in the Eylea group had endoscopy upper gastrointestinal tract and nail operation.

Overall, 18 (4.4%) subjects (Mynzepli: 7 [3.4%]; Eylea: 11 [5.4%]) were reported with at least 1 concomitant non-ocular procedure up to Week 24. Two (1%) subjects in Mynzepli group had transurethral prostatectomy. All other non-ocular surgeries or procedures up to Week 24 were reported in 1 subject in either of the treatment groups.

Both treatment arms were globally similar regarding prior/concomitant medications and procedure. The requested tables for prior and concomitant medications/procedures in the study and fellow eye have been provided in the clinical study report.

Numbers analysed

• Entered Analysis Set: A total of 856 subjects signed the ICF.

• Randomly Assigned to Study Treatment Set: Out of 856 subjects in the Entered Set, 413 subjects (Mynzepli: 206; Eylea: 207) were assigned to the study treatment.

• Full Analysis Set: Out of 413 subjects in the Randomly Assigned to Study Treatment Set, 410 subjects (Mynzepli: 205; Eylea: 205) were randomly assigned to the study treatment and received at least 1 dose of randomized study treatment in the study eye (Mynzepli or Eylea). The remaining 3 subjects (#160401, 210309 and 250147) were randomized in error; these subjects were allocated the study treatment; however, did not receive at least one dose of randomized study treatment in the study eye (hence these 3 subjects were not included in the FAS). All efficacy analyses were based on the FAS.

• Safety Analysis Set: All 410 subjects were randomly assigned to the study treatment and received at least one dose of study treatment. The safety analyses were based on the SAF.

• Pharmacokinetic Analysis Set: A total of 24 subjects (Mynzepli: 8; Eylea: 16) received at least one dose of the study treatment and had at least one PK result.

Table 18: Study Analysis Sets (Randomly Assigned to Study Treatment Set)

Description	AVT06 (N=206) n (%)	Eylea (N=207) n (%)	Total (N=413) n (%)
Subjects in the Randomly Assigned to Study Treatment Set	206 (100.0)	207 (100.0)	413 (100.0)
Subjects in the Full Analysis Set	205 (99.5)	205 (99.0)	410 (99.3)
Subjects in the Safety Analysis Set	205 (99.5)	205 (99.0)	410 (99.3)
Subjects in the Pharmacokinetic Analysis Set	8	16	24

Abbreviations: FAS=Full Analysis Set, n=Number of subjects.

Percentages were based on the total number of subjects in the Randomly Assigned to Study Treatment Set per treatment group.

Randomly Assigned to Study Treatment Set comprised of all subjects who signed informed consent and were assigned to study treatment. Full Analysis Set comprised of all subjects randomly assigned to study treatment and who received at least one dose of randomized study treatment in the study eye. Safety Analysis Set comprised of all subjects randomly assigned to study treatment and who received at least one dose of study treatment. Pharmacokinetic Analysis Set was a subset of subjects recruited who received at least one dose of study treatment and had at least one pharmacokinetic result.

Subject 160401 (rescreened as subject ID 160403), 210309, and 250147 were randomized in error. These subjects were allocated study treatment however did not receive at least one dose of randomized study treatment in the study eye so were not included in FAS.

Subject 110501 and 270204 were enrolled, randomized, and dosed with study drug in error. These subjects were in the FAS but did not contribute to the primary efficacy endpoint analysis.

Subject 160401 was a screen failure however was randomized in error. This subject was rescreened as Subject 160403 and randomized again. Both subjects are included in this table.

Data cut-off =16 April 2024.

Outcomes and estimation

Primary Efficacy Endpoint

The primary efficacy endpoint was change from baseline to Week 8 in BCVA as measured by ETDRS letter score. In order to provide the most sensitive analysis set to detect potential differences between Mynzepli and Eylea, the subject data impacted by the occurrence of any of the ICEs were excluded from the main analysis for the primary endpoint in FAS.

Table 19: Change from Baseline to Week 8 in BCVA as Measured by ETDRS Letter Score by Treatment Group Excluding the Data Impacted by the Occurrence of ICEs (FAS)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)
Week 8	n	203	201
	Mean (SD)	6.4 (7.92)	5.7 (8.86)
	Median	6.0	5.0
	Q1, Q3	0.0, 12.0	1.0, 11.0
	Min, Max	-16, 31	-36, 32
	m	204	203
	LS Mean [SE]	5.11 [0.677]	4.34 [0.687]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.77 [0.829]
	(90% CI)		(-0.60, 2.14)
	(95% CI)		(-0.86, 2.40)

Abbreviations: BCVA=Best-Corrected Visual Acuity, CI=confidence interval, ETDRS=Early Treatment Diabetic Retinopathy Study, FAS= Full Analysis Set, ICE=intercurrent event, LS=least squares, m=number of subjects with non-missing data at Week 4 or Week 8, max=maximum, min=minimum, n=number of subjects with non-missing data, Q1=1st quartile, Q3=3rd quartile, SD=standard deviation, SE=standard error.

Notes: LS means were estimated from a mixed effects model for repeated measures including BCVA at baseline as a continuous covariate, geographical origin, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects. An unstructured covariance structure was used to model the within subject error with an adjustment to the degrees of freedom using the Kenward Roger's approximation. Confidence intervals were estimated by the difference in LS means from the treatment-by-visit interaction.

If the CIs were completely contained within the equivalence margin of [-3.5 to 3.5], a therapeutic equivalence was demonstrated.

Following are the details on exclusion of subject's data from the primary endpoint analysis:

Subject 180203, Week 8 assessment was excluded from the primary endpoint analysis due to the data being impacted by the occurrence of ICEs (Week 8 visit not performed).

Subject 110406, excluded from the primary endpoint analysis due to the data being impacted by the occurrence of ICEs (Week 4 and Week 8 assessment not performed).

Subject 110911 and 170522, Week 8 visit was not performed, therefore only baseline and Week 4 assessment was used in the primary endpoint analysis. The Week 8 visit was not impacted by the occurrence of ICEs.

Subject 110501 and 270204, excluded from the primary endpoint analysis due to the data being impacted by the occurrence of ICEs (violated the inclusion criteria).

Data cut-off=16 April 2024.

Sensitivity Analysis

Sensitivity analysis for the primary endpoint was performed using the same analytical approach as for the main analysis based on the FAS, without exclusion of any data for subjects with any of the ICEs specified for the main estimator.

Table 20: Change from Baseline to Week 8 in BCVA as Measured by ETDRS Letter Score Regardless of the Occurrence of ICE by Treatment Group (FAS)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)
Week 8	n	204	202
	Mean (SD)	6.3 (7.95)	5.8 (9.03)
	Median	6.0	5.0
	Q1, Q3	0.0, 12.0	1.0, 11.0
	Min, Max	-16, 31	-36, 32
	m	205	204
	LS Mean [SE]	5.14 [0.685]	4.57 [0.694]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.56 [0.838]
	(90% CI)		(-0.82, 1.94)
	(95% CI)		(-1.08, 2.21)

Abbreviations: BCVA=Best-Corrected Visual Acuity, CI=confidence interval, ETDRS=Early Treatment Diabetic Retinopathy Study, FAS=Full Analysis Set, ICE=intercurrent event, LS=least squares, m=number of subjects with non-missing data at Week 4 or Week 8, max=maximum, min=minimum, n=number of subjects with non-missing data, Q1=1st quartile, Q3=3rd quartile, SD=standard deviation, SE=standard error.

LS means were estimated from a mixed effects model for repeated measures including BCVA at baseline as a continuous covariate, geographical origin, iris color, treatment, visit, and treatment-by-visit interaction as fixed effects. An unstructured covariance structure was used to model the within subject error with an adjustment to the degrees of freedom using the Kenward Roger's approximation. Confidence intervals were estimated by the difference in LS means from the treatment-by-visit interaction.

Data cut-off=16 April 2024.

Secondary Efficacy Endpoints

Change from baseline in BCVA as assessed by ETDRS letter score at Week 4, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52.

Table 21: Change from Baseline to Study Visits in BCVA in Study Eye as Measured by ETDRS Letter Score by Treatment Group (FAS)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)
Week 4	n	205	204
	Mean (SD)	4.4 (7.37)	4.0 (7.17)
	Median	4.0	3.0
	Q1, Q3	0.0, 9.0	0.0, 7.0
	Min, Max	-26, 27	-20, 30
	LS Mean [SE]	3.15 [0.611]	2.67 [0.619]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.48 [0.709]
	(95% CI)		(-0.92, 1.87)
Week 8	n	204	202
	Mean (SD)	6.3 (7.95)	5.8 (9.03)
	Median	6.0	5.0
	Q1, Q3	0.0, 12.0	1.0, 11.0
	Min, Max	-16, 31	-36, 32
	LS Mean [SE]	5.45 [0.724]	4.88 [0.738]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.57 [0.842]
	(95% CI)		(-1.09, 2.22)
Week 16	n	201	194
	Mean (SD)	7.2 (10.04)	7.3 (10.13)
	Median	7.0	7.5
	Q1, Q3	1.0, 12.0	1.0, 15.0
	Min, Max	-45, 39	-31, 32
	LS Mean [SE]	6.44 [0.859]	6.33 [0.879]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.12 [1.005]
	(95% CI)		(-1.86, 2.09)
Week 24	n	197	194
	Mean (SD)	7.2 (11.66)	8.2 (10.54)
	Median	7.0	8.0
	Q1, Q3	1.0, 14.0	1.0, 14.0
	Min, Max	-44, 39	-23, 36
	LS Mean [SE]	6.22 [0.961]	7.08 [0.979]
	LS Mean Difference (AVT06 - Eylea) [SE]		-0.86 [1.116]
	(95% CI)		(-3.05, 1.34)

Abbreviations: ANCOVA=analysis of covariance, BCVA=Best-Corrected Visual Acuity, CI=confidence interval, ETDRS=Early Treatment Diabetic Retinopathy Study, FAS=Full Analysis Set, LS=least squares, max=maximum, min=minimum, n=number of subjects with non-missing data, Q1=1st quartile, Q3=3rd quartile, SD=standard deviation, SE=standard error.

LS means at each visit were estimated from an ANCOVA model including geographical origin, iris color and treatment as factors, and the BCVA at baseline as a continuous covariate.

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)
	(95% CI)		(-3.05, 1.34)
Week 32	n	197	195
	Mean (SD)	7.5 (12.25)	8.7 (11.63)
	Median	7.0	8.0
	Q1, Q3	1.0, 14.0	2.0, 16.0
	Min, Max	-38, 40	-23, 41
	LS Mean [SE]	6.51 [1.029]	7.57 [1.046]
	LS Mean Difference (AVT06 - Eylea) [SE]		-1.06 [1.193]
	(95% CI)		(-3.41, 1.28)
Week 40	n	195	186
	Mean (SD)	7.8 (12.03)	9.2 (11.34)
	Median	7.0	9.0
	Q1, Q3	1.0, 15.0	3.0, 16.0
	Min, Max	-40, 37	-24, 41
	LS Mean [SE]	7.08 [1.015]	8.04 [1.040]
	LS Mean Difference (AVT06 - Eylea) [SE]		-0.96 [1.181]
	(95% CI)		(-3.28, 1.36)
Week 48	n	191	187
	Mean (SD)	7.9 (12.39)	9.5 (12.15)
	Median	8.0	10.0
	Q1, Q3	1.0, 16.0	4.0, 18.0
	Min, Max	-35, 34	-27, 41
	LS Mean [SE]	7.23 [1.065]	8.50 [1.072]
	LS Mean Difference (AVT06 - Eylea) [SE]		-1.27 [1.237]
	(95% CI)		(-3.70, 1.16)
Week 52	n	191	189
	Mean (SD)	8.3 (12.47)	9.4 (13.28)
	Median	10.0	10.0
	Q1, Q3	1.0, 17.0	3.0, 17.0
	Min, Max	-36, 35	-58, 41
	LS Mean [SE]	7.11 [1.106]	7.79 [1.118]
	LS Mean Difference (AVT06 - Eylea) [SE]		-0.67 [1.289]
	(95% CI)		(-3.21, 1.86)

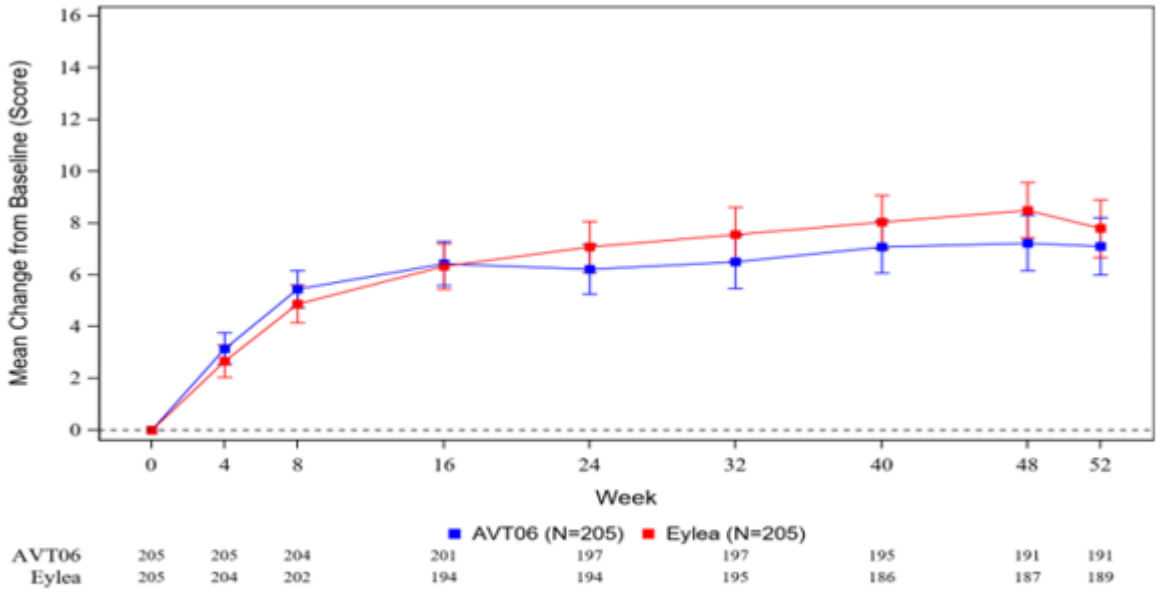
Abbreviations: ANCOVA=analysis of covariance, BCVA=Best corrected Visual Acuity, CI=confidence interval, ETDRS=Early Treatment Diabetic Retinopathy Study, FAS=Full Analysis Set, LS=least squares, max=maximum, min=minimum, n=number of subjects with non-missing data, Q1=1st quartile, Q3=3rd quartile, SD=standard deviation, SE=standard error.

LS means at each visit were estimated from an ANCOVA model including geographical origin, iris color and treatment as factors, and the BCVA at baseline as a continuous covariate.

Data cut-off=Database locked and final.

Source: Table 14.2.1.3; Listing 16.2.6.2.

Figure 8: Least Squares Mean (Standard Error) Change from Baseline to Study Time by treatment in BCVA Letter Score up to Week 52(FAS)



Source: Module 5.3.5.1, Final CSR, AVT06-GL-C01, Figure 14.2.1.10b
BCVA: Best Corrected Visual Acuity, ETDRS: Early Treatment Diabetic Retinopathy Study.

Gain or Loss of ê5, 10, 15 letter score in BCVA from baseline to Week 4, Week 8, Week 16, and Week 24, Week 32, Week 40, Week 48 and Week 52

Table 22: Subjects with gain of ⩾ 5, 10, 15 Letter Score in BCVA from Baseline to Study Visits in Study Eye (FAS)

Study Visit	Gain in Letter Score	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
Week 4	≥5	n (%)	56 (27.3)	44 (21.6)	100 (24.4)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.02 (-0.01, 0.06)
	≥10	n (%)	27 (13.2)	22 (10.8)	49 (12.0)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥15	n (%)	17 (8.3)	18 (8.8)	35 (8.6)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
Week 8	≥5	n (%)	49 (24.0)	43 (21.3)	92 (22.7)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.03, 0.05)
	≥10	n (%)	31 (15.2)	38 (18.8)	69 (17.0)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.04, 0.01)
	≥15	n (%)	36 (17.6)	27 (13.4)	63 (15.5)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.03 (-0.01, 0.07)
Week 16	≥5	n (%)	49 (24.4)	39 (20.1)	88 (22.3)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.02 (-0.03, 0.06)
	≥10	n (%)	24 (11.9)	29 (14.9)	53 (13.4)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.04, 0.02)
	≥15	n (%)	44 (21.9)	49 (25.3)	93 (23.5)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.05, 0.03)
Week 24	≥5	n (%)	44 (22.3)	38 (19.6)	82 (21.0)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.03, 0.05)
	≥10	n (%)	31 (15.7)	38 (19.6)	69 (17.6)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.06, 0.01)
	≥15	n (%)	45 (22.8)	47 (24.2)	92 (23.5)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.04, 0.04)
Week 32	≥5	n (%)	47 (23.9)	41 (21.0)	88 (22.4)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.03, 0.05)
	≥10	n (%)	32 (16.2)	33 (16.9)	65 (16.6)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.04, 0.03)
	≥15	n (%)	47 (23.9)	56 (28.7)	103 (26.3)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.06, 0.02)
Week 40	≥5	n (%)	46 (23.6)	39 (21.0)	85 (22.3)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.03, 0.05)
	≥10	n (%)	29 (14.9)	36 (19.4)	65 (17.1)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.03 (-0.06, 0.01)
	≥15	n (%)	51 (26.2)	53 (28.5)	104 (27.3)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.04, 0.04)
Week 48	≥5	n (%)	41 (21.5)	38 (20.3)	79 (20.9)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.04, 0.04)
	≥10	n (%)	29 (15.2)	36 (19.3)	65 (17.2)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.06, 0.01)
	≥15	n (%)	55 (28.8)	61 (32.6)	116 (30.7)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.05, 0.03)
Week 52	≥5	n (%)	29 (15.2)	36 (19.0)	65 (17.1)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.05, 0.01)
	≥10	n (%)	39 (20.4)	37 (19.6)	76 (20.0)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.04, 0.04)
	≥15	n (%)	58 (30.4)	63 (33.3)	121 (31.8)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.04, 0.04)

Abbreviations: BCVA=Best corrected Visual Acuity, CI=confidence interval, ETDRS=Early Treatment Diabetic Retinopathy Study, FAS=Full Analysis Set, n=Number of subjects, NC=not calculable.

Notes: Gain in letter score counts were mutually exclusive, ie, subjects were counted in one category only per study visit. BCVA was measured by ETDRS letter score. Percentages were based on the total number of subjects in the FAS per treatment group with non-missing data at the visit.

Difference in proportions were estimated using a logistic regression with BCVA at baseline as continuous covariate, geographical origin, iris color, and treatment as factors. The delta method was used to derive the covariate-adjusted difference in proportions between treatment groups and the associated 95% CIs for the difference.

Not calculable (NC) is presented in place of the estimated difference in proportion for models which did not converge.

Data cut-off=Database locked and final.

Source: Table 14.2.1.6; Listing 16.2.6.2.

Table 23: Subjects with loss of ⩾ 5, 10, 15 Letter Score in BCVA from Baseline to Study Visits in Study Eye (FAS)

Study Visit	Loss in Letter Score	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
Week 4	≥5	n (%)	8 (3.9)	11 (5.4)	19 (4.6)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.03, 0.01)
	≥10	n (%)	4 (2.0)	3 (1.5)	7 (1.7)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.02, 0.03)
	≥15	n (%)	3 (1.5)	3 (1.5)	6 (1.5)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
Week 8	≥5	n (%)	12 (5.9)	10 (5.0)	22 (5.4)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.02, 0.03)
	≥10	n (%)	2 (1.0)	5 (2.5)	7 (1.7)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥15	n (%)	1 (0.5)	4 (2.0)	5 (1.2)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
Week 16	≥5	n (%)	7 (3.5)	7 (3.6)	14 (3.5)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.02, 0.02)
	≥10	n (%)	4 (2.0)	3 (1.5)	7 (1.8)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥15	n (%)	2 (1.0)	5 (2.6)	7 (1.8)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
Week 24	≥5	n (%)	7 (3.6)	7 (3.6)	14 (3.6)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥10	n (%)	5 (2.5)	6 (3.1)	11 (2.8)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥15	n (%)	7 (3.6)	4 (2.1)	11 (2.8)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
Week 32	≥5	n (%)	10 (5.1)	13 (6.7)	23 (5.9)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥10	n (%)	7 (3.6)	5 (2.6)	12 (3.1)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥15	n (%)	8 (4.1)	6 (3.1)	14 (3.6)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.02, 0.03)
Week 40	≥5	n (%)	14 (7.2)	10 (5.4)	24 (6.3)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥10	n (%)	4 (2.1)	5 (2.7)	9 (2.4)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥15	n (%)	8 (4.1)	4 (2.2)	12 (3.1)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
Week 48	≥5	n (%)	15 (7.9)	9 (4.8)	24 (6.3)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.02 (-0.01, 0.06)
	≥10	n (%)	6 (3.1)	6 (3.2)	12 (3.2)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
	≥15	n (%)	9 (4.7)	7 (3.7)	16 (4.2)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			NC (NC, NC)
Week 52	≥5	n (%)	15 (7.9)	9 (4.8)	24 (6.3)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.02 (-0.01, 0.06)
	≥10	n (%)	7 (3.7)	4 (2.1)	11 (2.9)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.02, 0.04)
	≥15	n (%)	8 (4.2)	9 (4.8)	17 (4.5)
		Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.03, 0.02)

Abbreviations: BCVA=Best corrected Visual Acuity, CI=confidence interval, FAS=Full Analysis Set, ETDRS=Early Treatment Diabetic Retinopathy Study, n=Number of subjects, NC=not calculable.

Notes: Loss in letter score counts were mutually exclusive, ie, subjects were counted in one category only per study visit. BCVA was measured by ETDRS letter score. Percentages are based on the total number of subjects in the FAS per treatment group with non-missing data at the visit. Difference in proportions were estimated using a logistic regression with BCVA at baseline as continuous covariate, geographical origin, iris color, and treatment as factors. The delta method was used to derive the covariate-adjusted difference in proportions between treatment groups and the associated 95% CIs for the difference. Not calculable (NC) is presented in place of the estimated difference in proportion for models which did not converge. Data cut-off=Database locked and final. Source: Table 14.2.1.7; Listing 16.2.6.2.

Change from Baseline in CST as assessed by SD-OCT to Week 4, Week 8, Week 16, and Week 24 Week 32, Week 40, Week 48 and Week 52

Table 24: Change from Baseline to Study Visits in Central Subfield Thickness in Study Eye as assessed by Spectral Domain Optical Coherence Tomography by Treatment Group (FAS)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)
Week 4	n	200	200
	Mean (SD)	-156.8 (111.26)	-159.7 (107.06)
	Median	-130.5	-131.5
	Q1, Q3	-215.0, -84.0	-226.0, -84.0
	Min, Max	-589, 45	-525, 54
	LS Mean [SE]	-162.3 [8.79]	-158.9 [8.89]
	LS Mean Difference (AVT06 - Eylea) [SE]		-3.3 [10.21]
	(95% CI)		(-23.4, 16.7)
Week 8	n	197	196
	Mean (SD)	-171.1 (116.09)	-178.1 (108.52)
	Median	-148.0	-150.0
	Q1, Q3	-226.0, -100.0	-239.5, -98.5
	Min, Max	-590, 55	-548, 16
	LS Mean [SE]	-178.7 [9.03]	-179.7 [9.16]
	LS Mean Difference (AVT06 - Eylea) [SE]		1.0 [10.51]
	(95% CI)		(-19.6, 21.7)
Week 16	n	194	188
	Mean (SD)	-158.1 (122.55)	-165.5 (118.20)
	Median	-131.5	-135.0
	Q1, Q3	-222.0, -78.0	-246.0, -85.5
	Min, Max	-595, 91	-521, 100
	LS Mean [SE]	-168.3 [9.80]	-169.1 [10.06]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.8 [11.42]
	(95% CI)		(-21.7, 23.3)
Week 24	n	191	188
	Mean (SD)	-162.1 (126.72)	-168.3 (116.56)
	Median	-136.0	-144.5
	Q1, Q3	-226.0, -78.0	-235.0, -84.5
	Min, Max	-641, 179	-536, 63
	LS Mean [SE]	-175.1 [10.02]	-174.0 [10.15]
	LS Mean Difference (AVT06 - Eylea) [SE]		-1.1 [11.61]

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)
	(95% CI)		(-24.0, 21.7)
Week 32	n	190	188
	Mean (SD)	-177.3 (129.25)	-181.2 (118.14)
	Median	-151.0	-159.5
	Q1, Q3	-243.0, -96.0	-253.0, -97.5
	Min, Max	-648, 141	-544, 98
	LS Mean [SE]	-185.8 [10.01]	-181.7 [10.13]
	LS Mean Difference (AVT06 - Eylea) [SE]		-4.1 [11.60]
	(95% CI)		(-26.9, 18.7)
Week 40	n	191	180
	Mean (SD)	-181.9 (133.98)	-183.5 (119.42)
	Median	-152.0	-164.5
	Q1, Q3	-264.0, -85.0	-257.0, -98.5
	Min, Max	-660, 232	-531, 54
	LS Mean [SE]	-191.6 [10.44]	-183.7 [10.72]
	LS Mean Difference (AVT06 - Eylea) [SE]		-7.9 [12.15]
	(95% CI)		(-31.8, 16.0)
Week 48	n	184	181
	Mean (SD)	-187.8 (136.30)	-184.5 (121.38)
	Median	-158.0	-166.0
	Q1, Q3	-265.5, -98.0	-257.0, -102.0
	Min, Max	-663, 269	-535, 81
	LS Mean [SE]	-200.0 [10.56]	-184.8 [10.54]
	LS Mean Difference (AVT06 - Eylea) [SE]		-15.2 [12.24]
	(95% CI)		(-39.3, 8.9)
Week 52	n	183	181
	Mean (SD)	-204.9 (129.84)	-202.8 (120.50)
	Median	-167.0	-177.0
	Q1, Q3	-290.0, -121.0	-275.0, -119.0
	Min, Max	-661, -8	-597, 124
	LS Mean [SE]	-215.3 [10.07]	-200.5 [10.10]
	LS Mean Difference (AVT06 - Eylea) [SE]		-14.8 [11.70]
	(95% CI)		(-37.8, 8.2)

Abbreviations: ANCOVA=Analysis of Covariance, BCVA=Best corrected Visual Acuity, n=number of subjects with non-missing data, CI=confidence interval, FAS= Full Analysis Set, LS=Least Squares, max=maximum, min=minimum, Q1=1st quartile, Q3=3rd quartile, SD=standard deviation, SE=Standard Error.

Notes: LS means at each visit were estimated from an ANCOVA model including geographical origin, iris color and treatment as factors, and the BCVA at baseline as a continuous covariate.

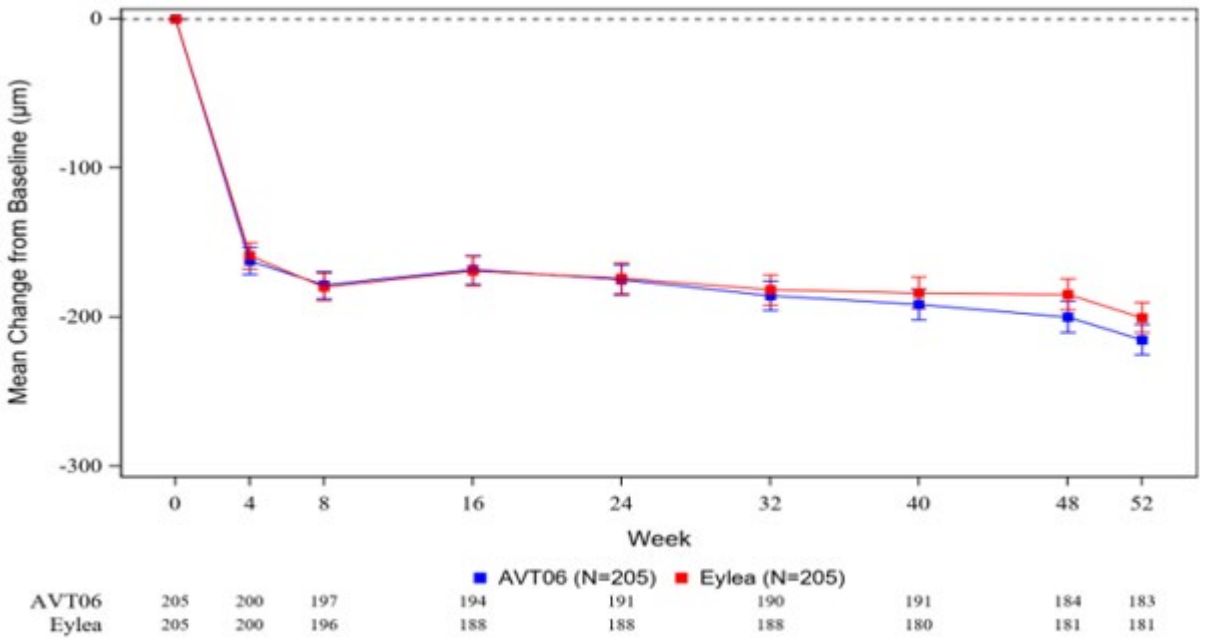
A negative change value indicates an improvement, while a positive change value indicates a worsening. One eye (study eye) contributed to the analysis.

Central subfield thickness was recorded in µm.

Data cut-off=Database locked and final.

Source: Table 14.2.1.4; Listing 16.2.6.5.

Table 25: Least Squares Mean (Standard Error) Change from Baseline to Study Time by treatment in Central Subfield Thickness up to Week 52 (FAS)



Change from baseline in Choroidal Neovascularization Area as Assessed by Fluorescein Angiography and Color Fundus Photography to Week 8, Week 24 and Week 52.

Table 26: Change from Baseline to Study Visits in Choroidal Neovascularization Area in Study Eye as Assessed by Fluorescein Angiography and Color Fundus Photography by Treatment Group (FAS)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)
Week 8			
Fluorescent angiography	n	185	174
	Mean (SD)	-0.056 (1.8307)	-0.030 (1.9009)
	Median	-0.080	-0.220
	Q1, Q3	-0.810, 0.690	-0.830, 0.400
	Min, Max	-7.89, 7.66	-4.92, 7.48
	LS Mean [SE]	0.03 [0.169]	0.05 [0.172]
	LS Mean Difference (AVT06 - Eylea) [SE]		-0.02 [0.198]
	(95% CI)		(-0.41, 0.37)
Fundus photography	n	185	174
	Mean (SD)	-0.052 (1.8310)	0.002 (1.9489)
	Median	-0.080	-0.220
	Q1, Q3	-0.810, 0.710	-0.810, 0.400
	Min, Max	-7.89, 7.66	-4.92, 9.02
	LS Mean [SE]	0.03 [0.171]	0.08 [0.174]
	LS Mean Difference (AVT06 - Eylea) [SE]		-0.04 [0.201]
	(95% CI)		(-0.44, 0.35)
Week 24			
Fluorescent angiography	n	175	174
	Mean (SD)	-0.086 (2.9586)	-0.443 (2.6268)
	Median	-0.070	-0.425
	Q1, Q3	-1.040, 1.050	-1.340, 0.480
	Min, Max	-10.79, 17.61	-15.55, 8.92
	LS Mean [SE]	-0.06 [0.264]	-0.41 [0.264]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.35 [0.303]
	(95% CI)		(-0.24, 0.95)
Fundus Photography	n	174	173
	Mean (SD)	-0.082 (2.9664)	-0.414 (2.6508)
	Median	-0.065	-0.420
	Q1, Q3	-1.030, 1.050	-1.230, 0.480
	Min, Max	-10.79, 17.61	-15.55, 8.92
	LS Mean [SE]	-0.05 [0.267]	-0.38 [0.266]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.33 [0.306]
	(95% CI)		(-0.27, 0.93)

Abbreviations: ANCOVA=analysis of covariance, BCVA=Best-Corrected Visual Acuity, CI=confidence interval, FAS=Full Analysis Set, LS=least squares, max=maximum, min=minimum, n=number of subjects with non-missing data, Q1=1st quartile, Q3=3rd quartile, SD=standard deviation, SE=standard error.

Notes: LS means at each visit were estimated from an ANCOVA model including geographical origin, iris color and treatment as factors, and the BCVA at baseline as a continuous covariate.

A negative change value indicates an improvement, while a positive change value indicates a worsening. One eye (study eye) contributed to the analysis.

Choroidal neovascularization area unit is square millimeter (mm^2).

Data cut-off=16 April 2024.

Week 52			
Fluorescent Angiography	n	155	142
	Mean (SD)	-2.807 (4.5875)	-3.166 (4.9652)
	Median	-1.470	-1.705
	Q1, Q3	-4.330, -0.190	-5.660, -0.030
	Min, Max	-18.00, 8.99	-22.00, 7.44
	LS Mean [SE]	-2.75 [0.470]	-2.96 [0.485]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.22 [0.552]
	(95% CI)		(-0.87, 1.30)
Fundus Photography	n	155	142
	Mean (SD)	-2.805 (4.5886)	-3.127 (5.0069)
	Median	-1.470	-1.705
	Q1, Q3	-4.330, -0.180	-5.660, -0.030
	Min, Max	-18.00, 8.99	-22.00, 8.36
	LS Mean [SE]	-2.74 [0.473]	-2.92 [0.487]
	LS Mean Difference (AVT06 - Eylea) [SE]		0.18 [0.555]
	(95% CI)		(-0.91, 1.28)

Abbreviations: ANCOVA=analysis of covariance, BCVA=Best corrected Visual Acuity, CI=confidence interval, FAS=Full Analysis Set, LS=least squares, max=maximum, min=minimum, n=number of subjects with non-missing data, Q1=1st quartile, Q3=3rd quartile, SD=standard deviation, SE=standard error.

Notes: LS means at each visit were estimated from an ANCOVA model including geographical origin, iris color and treatment as factors, and the BCVA at baseline as a continuous covariate.

A negative change value indicates an improvement, while a positive change value indicates a worsening. One eye (study eye) contributed to the analysis.

Choroidal neovascularization area unit is square millimeter (mm^2).

Data cut-off=Database locked and final.

Source: Table 14.2.1.5; Listing 16.2.6.6.

Absence of Intra-retinal Fluid from Baseline to Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52

Table 27: Absence of Intra-retinal Fluid from Baseline to Each Week in Study Eye (FAS)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
Week 4	n (%)	56 (35.4)	47 (31.5)	103 (33.6)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.02 (-0.04, 0.07)
Week 8	n (%)	64 (41.0)	62 (42.2)	126 (41.6)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.07, 0.04)
Week 16	n (%)	49 (32.0)	50 (35.7)	99 (33.8)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.03 (-0.08, 0.03)
Week 24	n (%)	56 (36.8)	55 (39.6)	111 (38.1)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.08, 0.03)
Week 32	n (%)	54 (36.0)	52 (37.1)	106 (36.6)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.01 (-0.07, 0.04)
Week 40	n (%)	53 (35.3)	47 (34.8)	100 (35.1)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.00 (-0.06, 0.05)
Week 48	n (%)	45 (31.0)	47 (35.1)	92 (33.0)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.03 (-0.08, 0.02)
Week 52	n (%)	74 (51.7)	61 (44.2)	135 (48.0)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.03 (-0.03, 0.08)

Abbreviations: BCVA=Best corrected Visual Acuity, CI=confidence interval, FAS=Full Analysis Set, n=Number of subjects.

Notes: Percentages are based on the total number of subjects in the FAS per treatment group with non-missing data at the visit and presence of intra-retinal fluid at baseline.

Difference in proportions were estimated using a logistic regression with BCVA at baseline as continuous covariate, geographical origin, iris color, and treatment as factors. The delta method was used to derive the covariate-adjusted difference in proportions between treatment groups and the associated 95% CIs for the difference.

Data cut-off=Database locked and final

Source: Table 14.2.1.8; Listing 16.2.6.4.

Table 28: Absence of Subretinal Fluid from Baseline to Each Week in Study Eye (FAS)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
Week 4	n (%)	74 (38.7)	69 (35.9)	143 (37.3)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			0.01 (-0.03, 0.06)
Week 8	n (%)	99 (52.4)	108 (57.1)	207 (54.8)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.07, 0.03)
Week 16	n (%)	77 (41.6)	87 (47.8)	164 (44.7)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.03 (-0.08, 0.02)
Week 24	n (%)	86 (47.0)	95 (52.5)	181 (49.7)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.07, 0.03)
Week 32	n (%)	86 (47.5)	96 (52.5)	182 (50.0)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.07, 0.03)
Week 40	n (%)	86 (47.3)	91 (52.6)	177 (49.9)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.07, 0.03)
Week 48	n (%)	83 (47.4)	93 (53.8)	176 (50.6)

Study Visit	Statistic	AVT06 (N=205)	Eylea (N=205)	Total (N=410)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.02 (-0.08, 0.03)
Week 52	n (%)	106 (61.3)	121 (68.4)	227 (64.9)
	Estimated Difference in Proportion (AVT06 - Eylea) (95%)			-0.03 (-0.08, 0.02)

Abbreviations: BCVA=Best corrected Visual Acuity, CI=confidence interval, FAS=Full Analysis Set, n=Number of subjects, NC=not calculable.

Notes: Percentages are based on the total number of subjects in the FAS per treatment group with non-missing data at the visit and presence of subretinal fluid at baseline.

Difference in proportions were estimated using a logistic regression with BCVA at baseline as continuous covariate, geographical origin, iris color, and treatment as factors. The delta method was used to derive the covariate-adjusted difference in proportions between treatment groups and the associated 95% CIs for the difference.

Data cut-off=Database locked and final.

Source: Table 14.2.1.9; Listing 16.2.6.4.

The applicant suggests that the slight decrease in CST from Week 8 to Week 16 is most likely due to the fact that the Week 16 assessment occurred 8 weeks after the last study drug administration, while the assessments at Week 4 and Week 8 were conducted 4 weeks after the previous dose. Furthermore, regarding efficacy data on CST and the proportion of patients without intra- or sub-retinal fluid, it was observed that the data are comparable between the Mynzepli and Eylea groups at all-time points. The applicant uses mixed model for repeated measures (MMRM) for primary efficacy endpoint change from baseline to Week 8 in BCVA as measured by ETDRS letter score. Secondary efficacy endpoints also include change from baseline in BCVA as measured by ETDRS letter score, but with respect to other weeks (Week 4, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52, respectively). However, statistical analysis to other weeks is based on analysis of covariance model which differs from MMRM by structure of fixed effects and absence of random effect using unstructured covariance structure. The applicant provided requested calculations based on MMRM which extends analysis of primary endpoint to other weeks than only to Week 8. Equivalence of test product Mynzepli to

reference product Eylea is investigated with respect to equivalence range (ER) given by (-3.5 letters, 3.5 letters) for difference between Mynzepli and Eylea with respect to primary endpoint. If other visits are taken into account, then equivalence is concluded at Week 4, Week 8, Week 16, Week 24, Week 32 and Week 40, respectively, as 95% CI for difference between Mynzepli and Eylea is fully included within ER. On the other hand, equivalence is not concluded at Week 48 and Week 52, respectively, as 95% CI for difference between Mynzepli and Eylea is not fully included within ER (-3.5 letters, 3.5 letters). More specifically, estimated difference in letters with 95% CI in letters is -1.24 with (-3.76, 1.27) at Week 48 and -0.94 with (-3.54, 1.66) at Week 52, i.e., lower limit of each 95% CI is below -3.5.

The applicant suggests that the study is sufficiently powered to detect assumed treatment effect only with respect to primary endpoint change from baseline to Week 8 in BCVA as measured by ETDRS letter score. Assumptions are not posed for other study visits including Week 48, i.e., Week 4, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52, respectively. Moreover, changes from baseline to other study visits (Week 4, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52, respectively) in BCVA as measured by ETDRS letter score are presented as secondary endpoints with descriptive purpose. In case of descriptive purpose, consistency in results is usually demonstrated if point estimate for difference between Mynzepli and Eylea is within ER (-3.5 letters, 3.5 letters). Point estimate is within ER (-3.5 letters, 3.5 letters) for each study visit. Also, standard deviation increases both for Mynzepli and Eylea beyond Week 8 which can lead to insufficient statistical power (less than 80%) to conclude equivalence with respect to ER (-3.5 letters, 3.5 letters) taking into account that number of patients is formally derived only with respect to change from baseline to Week 8.

The applicant presented recalculation based on "hypothetical estimand strategy". However, after this recalculation the same situation occurred as in case of calculation based on "treatment policy strategy". More specifically, equivalence with respect to ER (-3.5 letters, 3.5 letters) is not concluded at Week 48 as 95% CI for difference between Mynzepli and Eylea is (-3.51 letters, 1.39 letter) and this 95% CI is not fully within ER (-3.5 letters, 3.5 letters). Similar argumentation for Week 48 can be applied also in case of "hypothetical estimand strategy". At first, study is not powered with respect to change from baseline to Week 48. At second, point estimate for difference between Mynzepli and Eylea lies fully within ER (-3.5 letters, 3.5 letters) as results based on other study visits are considered rather as descriptive.

The applicant uses logistic regression model (LRM) for assessment of proportion of patients with gain/loss of certain number of letters (at least 5, at least 10 and at least 15, respectively) from baseline to Week 4, Week 8, Week 16 and Week 24, respectively. Based on Appendix 6. SAS Code For Logistic Regression and Delta Method which can be found in Appendix 16.1.9. Documentation of Statistical Methods, LRM considers logit link function and covariate-adjusted absolute difference between proportions with corresponding 95% confidence interval is calculated by delta method. Query was raised regarding use of LRM with identity link function to evaluate absolute difference between proportions (treatments) instead of consideration of LRM with logit link function and delta method. Reasoning is that LRM with logit link function evaluates relative difference between proportions by odds ratio instead of absolute difference between proportions. However, this query was not properly answered by the applicant as abbreviation LRM was wrongly considered as abbreviation for linear regression model. Thus, query regarding use of LRM with identity link function prevails. The applicant justifies the estimation issue as known limitation of LRM with ILF because ILF is not constrained to produce predictions within close interval <0,1> compared to canonical link function given by logit link function. But at least for 12 available results based on use of LRM with ILF, results are consistent with use of LRM with logit link function combined with delta method.

Overall, the analyses of the primary and secondary efficacy endpoints tend to support the notion of similarity between Mynzepli and the reference product Eylea (aflibercept EU)

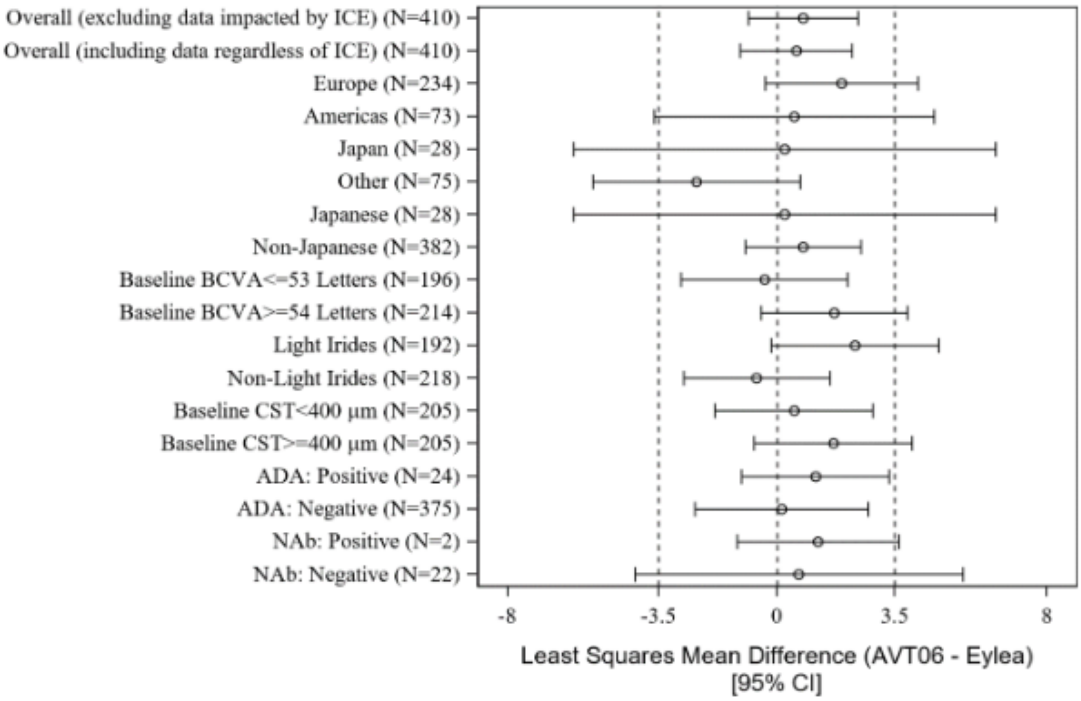
through 52 Weeks. As a response to the D120 LoQ, the applicant provided efficacy and safety data up to 52 weeks. Based on the results submitted equivalence between Mynzepli and Eylea is not concluded at Week 48 if analysis of covariance (ANCOVA) model for endpoint given by change from baseline to individual study visits in BCVA as measured by ETDRS letter score is considered. Corresponding 95% CI for difference between Mynzepli and Eylea at Week 48 is not fully included within ER (-3.5 letters, 3.5 letters). Moreover, it seems that results based on ANCOVA model are only provided for "treatment policy strategy" where analysis is based on FAS without exclusion of any data for subjects with any pre-specified intercurrent events (ICEs). However, there is also "hypothetical strategy" where analysis is based on FAS with exclusion of subject's data at and after the occurrence of any of pre-specified ICEs. Therefore, The applicant applied the same ICEs as those defined for the primary estimands. Accordingly, subjects' data following the occurrence of any of these ICEs were excluded from the ad hoc analysis of the secondary endpoint, using the same methodology as for the Week 8 primary endpoint analysis. According to the results provided by the applicant the 95% confidence intervals (CIs) for all time points fell within the predefined equivalence margins of [-3.5; 3.5], with one exception: a marginal breach of the lower 95% limit at Week 48 (-3.51). The LS mean difference (Mynzepli – Eylea) observed at this time point, amounting to 1.06 letters, represents the largest difference across all assessed time points. However, as mentioned above, it can be concluded that at Week 48, the change in LS mean BCVA letter score from baseline was comparable between the Mynzepli and Eylea groups.

Ancillary analyses

Subgroup analysis (Figure 3.3.4.2.23*)* was performed using similar Mixed model for repeated measures (MMRM) model for the primary analysis but excluding the respective subgroup as a fixed covariate: geographical origin (Europe, Americas, Japan, Other), geographical origin and race (Japanese, Non-Japanese), baseline BCVA (≤53 letters vs. ≥54 letters), iris color (light irides/non-light irides), baseline CST (<400.0 and ≥400.0 µm), ADA (positive/negative), and NAb (positive/negative).

The statistical analysis results of subgroups is considered descriptive. However, the results indicate differences in the following subgroups: geographical origin (Europe, Americas, Japan, Other), geographical origin and race (Japanese), baseline BCVA (≥54 letters), iris color (light irides), baseline CST (≥400.0 µm), and NAb (positive/negative).

Figure 9: Least Squares Mean Difference in Change from Baseline to Week 8 in BCVA Letter Score with 95% Confidence Interval (FAS)



Abbreviations: ADA=anti-drug antibodies, BCVA=Best-corrected Visual Acuity, CST=central subfield thickness, FAS=Full Analysis Set, ICE=intercurrent event, NAb=neutralizing antibody.

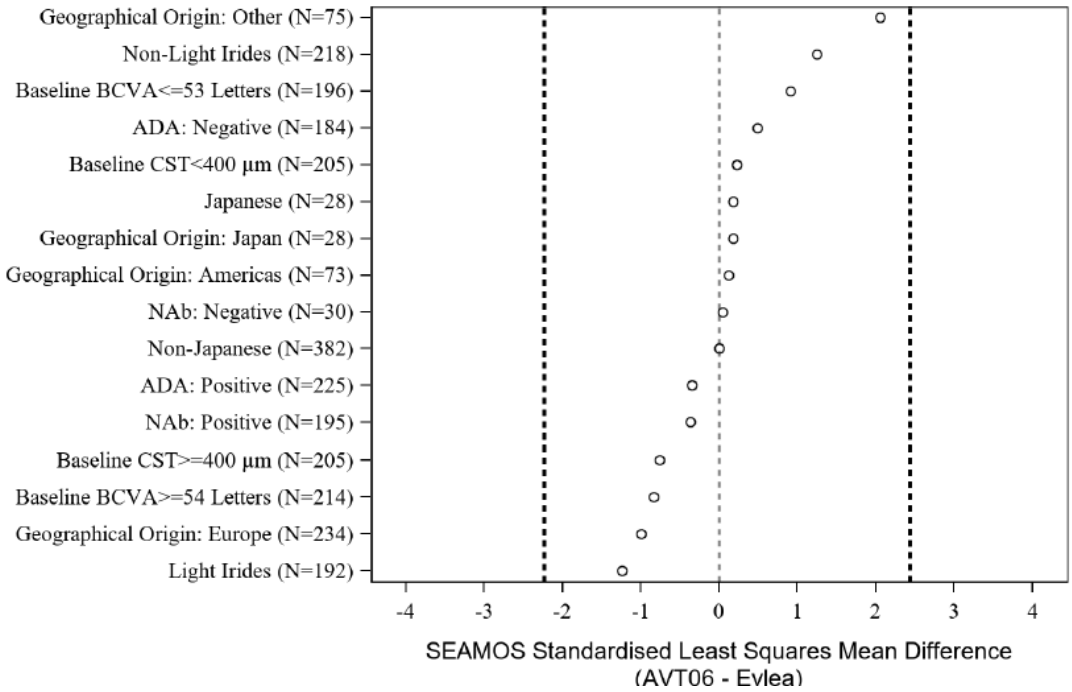
Results presented by subgroup excluded data impacted by the occurrence of ICEs.

Data cut-off=16 April 2024

Therefore, the applicant has been asked to discuss these finding both in statistical terms (e.g. with testing for interaction and SEAMOS' permuted estimates) and in terms of biological credibility.

The applicant pointed out that, considering high structural and functional similarity, there seems to be low biological credibility to these subgroups effects. Furthermore, the tests for interaction show no p-values smaller than 0.1, with the exception of a borderline result for the Iris Color (p-value = 0.0873), and – when applying the SEAMOS methodology - all of the standardised effects (also including non-light irides and light irides) are within the 2.5% and 97.5% percentile limits, suggesting that there is no subgroup heterogeneity.

Figure 10: SEAMOS standardised Least Square Mean Differences for subgroups of interest.



2.4.5.3. Summary of main efficacy results

The following tables summarise 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 29: Summary of efficacy for trial AVT06-GL-C01 - ALVOEYE

Title: AVT06-GL-C01 - ALVOEYE		
Study identifier	Study code AVT06-GL-C01 EU CT number 2021-003651-42 NCT number NCT05155293	
Design	Multicentre, randomized, double-masked, parallel-group, therapeutic equivalence Phase 3 study designed to evaluate the efficacy, safety, and immunogenicity of Mynzepli compared with Eylea in participants with neovascular (wet) AMD. The study also evaluated the systemic PK of Mynzepli and Eylea in a subset of participants.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable not applicable
Hypothesis	Equivalence	
Treatments groups	AVT06 (N=206 randomized)	Subjects randomized to Mynzepli were administered 2 mg/0.05 mL IVT injection using a single-dose vial every 4 weeks for 3 doses, then every 8 weeks for 5 doses (at week 16, 24, 32, 40, and 48), for a total of 52 weeks.

Title: AVT06-GL-C01 - ALVOEYE			
Study identifier	Study code AVT06-GL-C01 EU CT number 2021-003651-42 NCT number NCT05155293		
	EU-Eylea (N=207 randomized)	Subjects randomized to EU-Eylea were administered 2 mg/0.05 mL IVT injection using a single-dose vial every 4 weeks for 3 doses, then every 8 weeks for 5 doses (at week 16, 24, 32, 40, and 48), for a total of 52 weeks.	
Endpoints and definitions	Primary endpoint	Change from baseline in Best Corrected Visual Acuity using the ETDRS chart at Week 8	
Database lock	08 March 2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS)/ **PP (see OC)** **Week 8**		
Descriptive statistics and estimate variability	Treatment group	AVT06	EU-Eylea
	Number of subject	203	201
	Mean (SD)	6.4 (7.92)	5.7 (8.86)
	LSMeans (SE) of change from baseline in BCVA using EDTRS at Week 8	5.11 (0.6777)	4.34 (0.687)
	LSMean difference of Mynzepli – Eylea (SE) [95% CI]	0.77 (0.829) [-0.86; 2.40]	
Analysis description	**Sensitivity analysis of Primary Efficacy Variable**		
Analysis population and time point description	Full Analysis Set (FAS) / **PP (See OC)** **Week 8**		
Descriptive statistics and estimate variability	Treatment group	AVT06	EU-Eylea
	Number of subject	204	202
	Mean (SD)	6.3 (7.95)	5.8 (9.03)
	LSMeans (SE) of change from baseline in BCVA using EDTRS at Week 8	5.14 (0.685)	4.57 (0.694)
	LSMean difference of Mynzepli – Eylea (SE) [95% CI]	0.56 (0.838) [-1.08; 2.21]	

2.4.6. Discussion on clinical efficacy

Clinical development consisting of one pivotal study (study AVT06-GL-C01) in patients with wAMD was largely discussed in scientific advice (EMA/SA/0000063900) and deemed acceptable to determine biosimilarity of Mynzepli in adult indications approved for EU Eylea. This was a multicentre,

randomized, double-masked, parallel-group, therapeutic equivalence Phase 3 study designed to evaluate the efficacy, safety, and immunogenicity of Mynzepli compared with Eylea in participants with neovascular (wet) AMD during a period of 52 weeks (including 48 weeks of treatment).

Study design

Subjects were randomly assigned in a 1:1 ratio to receive study treatment via stratified randomization. The randomization was stratified by geographical origin (Europe, Americas, Japan, Other), baseline BCVA (Ḛ53 letters versus ệ54 letters), and iris color (light irides versus non-light irides). These subgroups were supposed to present potential heterogeneous responses to treatments that might interfere with the overall treatment effect. Additionally, the study was conducted in a double-masked manner with unmasked site staff who prepared the study treatment, given the difference in pharmaceutical form of Mynzepli (vial) and EU-Eylea (PFS). The EU-licenced Eylea was used as the comparator in the Phase 3 Study which is endorsed.

In the study eye, subjects received 2 mg (0.05 mL) IVT injection of Mynzepli or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1, Week 4, and Week 8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24, 32, 40, and 48). Subjects received a total of 8 IVT injections. The dosage regimen is consistent with the current EU-Eylea SmPC. Also, no dose modification and no rescue medication for the study eye were permitted.

The primary objective of the study was to demonstrate clinical equivalence of Mynzepli to EU-Eylea in term of BCVA score (using EDTRS testing charts) at 8 weeks and the secondary efficacy endpoints evaluated the change in BCVA, CST, CNV and presence/absence of intra/sub-retinal fluid from baseline at different time points over the study course are supported for the assessment of biosimilarity.

Analysis sets are considered adequate for clinical efficacy, sensitivity testing and safety control. The main analysis for the primary efficacy endpoint, change from baseline to Week 8 in BCVA measured by ETDRS letter score was based on mixed model for repeated measures (MMRM) with fixed effects given by BCVA at baseline, geographical origin, iris color, treatment, visit and treatment by visit interaction and with random effect given by subject using unstructured covariance structure to model within subject error. Moreover, the equivalence margins of ±3.5 letters for the EDTRS scale measuring the visual acuity represents less than one line difference in the EDTRS scale (5 letters by line), making the proposed equivalence interval clinically relevant.

Primary efficacy endpoint is analysed by two ways: 1) "hypothetical strategy" analysis which is based on full analysis set (FAS) with exclusion of subject's data at and after occurrence of intercurrent event (ICE) and 2) "treatment policy strategy" analysis which is based on FAS without exclusion of any subject's data.

Justification of both strategies is based on statements in ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017), section A.3.4. Considerations for Constructing an estimand, as study is equivalence study.

The study was conducted in treatment-naïve male and female patients of ệ 50 years, with a BCVA letters score assessed by EDTRS and comprised between 20/40 (upper limit) and 20/200 (lower limit), lesion area Ḛ 9 Disc Areas (DA), central retinal thickness of ệ300 µm in the study eye as determined by SD-OCT. Efficacy parameters assessed (BCVA score using ETDRS testing charts starting at 4 meters, CST using SD-OCT and confirmed by a CRC, CNV lesion using FA and color fundus photography) to demonstrate similar efficacy between Mynzepli and EU-Eylea adequately represent standards used for the respective assessments.

The study was initiated on June 2022 and conducted in 14 countries (Argentina, Brazil, Bulgaria, the Czech Republic, Georgia, Hungary, India, Japan, Latvia, Lithuania, Pakistan, Poland, Slovakia, and South Africa). The study was ongoing at the time of MAA submission and the applicant provided data up to 24 weeks (primary endpoint analysis).

A total of 884 subjects were screened (including 29 rescreened subjects), of which 413 subjects were randomized to the study treatment (205 subjects received AVT06, and 205 received EU-Eylea) and 472 subjects had screened failure. Among the 413 subjects, 394 subjects completed the study treatment up to Week 24. Moreover, the applicant provided justification for the reasons behind screen failures.

Overall, study treatment exposure (i.e. duration of exposure, compliance to study treatment) and the number of subjects in the FAS up to Week 24 are considered similar among the groups.

Protocol study was amendments four times (two of which were issued after screening) and are not considered to affect the efficacy interpretability of the study. Important protocol deviations are a subset of protocol deviations and was observed in 82 subjects (Mynzepli: 38; Eylea: 44) in the FAS. The most common important protocol deviations were related to the categories 'study procedures' (Mynzepli: 15; Eylea: 16 subjects), followed by 'randomization' (Mynzepli: 13; Eylea: 12 subjects), 'laboratory assessment' (Mynzepli: 7; Eylea: 9 subjects), and 'informed consent and process' (Mynzepli: 5; Eylea: 5 subjects). Globally, the proportion of subjects with protocol deviations were similar across the treatment groups. Additionally, there were four (1%) subjects (Mynzepli: 1; Eylea: 3) who had ICEs and protocol deviations that led to exclusion of data from the analysis for primary endpoint. 1 subject assigned to the Mynzepli was included in the study despite not meeting inclusion criterion 8. In the Eylea treatment group, two subjects missed visit at week 8 and one subject was enrolled and randomized despite not meeting eligibility criteria (INC06).

The following demographic characteristics at baseline were observed: more female patients were included in total (53.4%) than males, mean age across groups was 74 years, most participants were White (76.1%) and Asian (16.3%) and irides color was mostly non-light in 53.2% of subjects.

Overall, baseline disease characteristics are deemed similar between groups with a mean baseline BCVA letter score of was 55.8 in Mynzepli group and 55.2 in Eylea group. The mean (SD) CST observed was of 430.9 µm in Mynzepli group and 436.2 µm in Eylea group. The majority of subjects presented subretinal fluid (372 subjects in total) and 274 subjects in total presented intraretinal fluid. Baseline characteristics are deemed similar between Mynzepli and EU-Eylea groups for CNV lesion size (mm2) and IOP (mmHg).

Regarding history of medical conditions, ocular and non-ocular medical and surgical history was well balanced across treatment arms with:

- >10% of the subjects had the history of following ocular disorders in the study eye: cataract (Mynzepli: 90; Eylea: 103 subjects) and pseudophakia (Mynzepli: 20; Eylea: 26 subjects).

- >25% of the subjects had the history of following non-ocular disorders: vascular disorders (Mynzepli: 131; Eylea: 128 subjects), metabolism and nutrition disorders (Mynzepli: 88; Eylea: 90 subjects), and cardiac disorders (Mynzepli: 42; Eylea: 53 subjects).

Both treatment arms were globally similar regarding medical history, prior/concomitant medications and procedure. The requested tables for prior and concomitant medications/procedures in the study and fellow eye have been provided in the clinical study report.

Results

Primary efficacy analysis

The applicant's primary efficacy endpoint was the change from baseline to Week 8 in BCVA measured by ETDRS letter score. At week 8, the LS mean (SE) observed for change from baseline in BCVA was similar in both treatment groups (5.11 (0.677) and 4.34 (0.687) letters in Mynzepli and Eylea group, respectively). Both groups show an average gain of around one line of characters in visual acuity on the EDTRS scale. The LS mean (SE) difference in BCVA of the change from baseline between Mynzepli and Eylea at Week 8 was 0.77 (0.829) letters (90% CI of [-0.60, 2.14]; 95% CI of [-0.86, 2.40]), and was completely contained within the pre-defined equivalence margin of [−3.5 letters, 3.5 letters]. Therefore, the results show an efficacy equivalence between Mynzepli and Eylea.

The sensitivity analyses performed further strengthen the demonstration of the efficacy equivalence with regard to the primary endpoint. At week 8, the LS mean (SE) observed for change from baseline in BCVA was 5.14 (0.685) and 4.57 (0.694) letters in Mynzepli and Eylea group, respectively). The LS mean (SE) difference (Mynzepli - Eylea) in BCVA of the change from baseline to Week 8 was 0.56 (0.838) letters (90% CI of [-0.82, 1.94]; 95% CI of [-1.08, 2.21]).

Additionally, subgroup analysis was performed using similar Mixed model for repeated measures (MMRM) model for the primary analysis but excluding the respective subgroup as a fixed covariate: geographical origin (Europe, Americas, Japan, Other), geographical origin and race (Japanese, Non-Japanese), baseline BCVA (≤53 letters vs. ≥54 letters), iris color (light irides/non-light irides), baseline CST (<400.0 and ≥400.0 µm), ADA (positive/negative), and NAb (positive/negative).

The statistical analysis results of subgroups are considered descriptive. However, the results indicate differences in the following subgroups: geographical origin (Europe, Americas, Japan, Other), geographical origin and race (Japanese), baseline BCVA (≥54 letters), iris color (light irides), baseline CST (≥400.0 µm), and NAb (positive/negative). Therefore, the applicant was requested to further discuss these subgroup findings from both a statistical perspective (e.g., interaction testing and SEAMOS permuted estimates) and from the standpoint of biological plausibility. Considering the data provided by the applicant, the results indicate that there is no meaningful difference in treatment effect across the various subgroup categories (Week 8 change from baseline in BCVA (ETDRS letter score), by treatment group, excluding data influenced by ICEs; subgroup interaction assessed). Among these, the p-value for iris color (0.0873) was the closest to the significance threshold.

Moreover, considering the interaction testing and SEAMOS permuted estimates, the results indicate no evidence of subgroup heterogeneity, as all subgroups of interest fall within the 2.5% to 97.5% percentile limits.

Several secondary efficacy endpoints were assessed as follow:

Mean change in BCVA from baseline to Week 4, 8, 16, 24, 32, 40, 48, and 52

The mean changes in BCVA were similar between the treatment groups at the time points provided and showed a consistent increase in BCVA up to week 16 and appear to stabilize thereafter for Mynzepli contrary to what is observed in Eylea group at week 24. At baseline, the mean BCVA (± SD) was 55.8 (± 11.72) in Mynzepli group and 54.2 (± 12.35) letters in Eylea group. The mean (± SD) BCVA change from baseline to week 24 was 7.2 ± 11.66 and 11.1 ± 9.9 letters for Mynzepli and Eylea group respectively with a LS mean difference (Mynzepli –Eylea) of -0.86 letters and 95% CI [-3.05, 1.34].

Thus, equivalence is concluded at Week 4, Week 8, Week 16, Week 24, Week 32, Week 40 and Week 52, respectively, as 95% CI for difference is fully included within ER. More specifically, estimated difference in letters with 95% CI in letters is 0.48 with (-0.92, 1.87) at Week 4, 0.57 with (-1.09, 2.22) at Week 8, 0.12 with (-1.86, 2.09) at Week 16, -0.86 with (-3.05, 1.34) at Week 24, -1.06 with (-3.41, 1.28) at Week 32, -0.96 with (-3.28, 1.36) at Week 40 and -0.67 with (-3.21, 1.86) at Week 52.

Equivalence is concluded at Week 48 even if 95% CI for difference is not fully included within ER (-3.5 letters, 3.5 letters). Notably because the study is not powered with respect to change from baseline to Week 48.

Proportion of patients with gain or loss of ê 5, ê 10, and ê 15 ETDRS letters from baseline in BCVA to week 4, 8, 16, 24, 32, 40, 48 and 52

Overall, the proportion of patients with ệ 5, ệ 10, and ệ 15 ETDRS letters gain or loss was similar between the treatment groups at the different time points.

At week 24, the proportions of patients who gained ệ 5 (Mynzepli: 44 patients [22.3%]; Eylea: 38 patients [19.6%]), ệ 10 (Mynzepli: 31 patients [15.7%]; Eylea: 38 patients [19.6%]), and ệ 15 letters (Mynzepli: 45 patients [22.8%]; Eylea: 47 patients [24.2%]) were similar.

At week 24, the proportions of patients who lossed ≥ 5 (Mynzepli: 7 patients [3.6%]; Eylea: 7 patients [3.6%]), ≥ 10 (Mynzepli: 5 patients [2.5%]; Eylea: 6 patients [3.1%]), and ≥ 15 letters (Mynzepli: 7 patients [3.6%]; Eylea: 4 patients [2.1%]) were similar as well.

At week 52, the proportions of patients who gained ệ 5 (Mynzepli: 29 patients [15.2%]; Eylea: 36 patients [19.0%]), ệ 10 (Mynzepli: 39 patients [20.4%]; Eylea: 37 patients [19.6%]), and ệ 15 letters (Mynzepli: 58 patients [30.4%]; Eylea: 63 patients [33.3%]) were similar.

At week 52, the proportions of patients who loosed ệ 5 (Mynzepli: 15 patients [7.9%]; Eylea: 9 patients [4.8%]), ệ 10 (Mynzepli: 7 patients [3.7%]; Eylea: 4 patients [2.1%]), and ệ 15 letters (Mynzepli: 8 patients [4.2%]; Eylea: 9 patients [4.8%]) were similar as well.

Mean change in CST from baseline to Week 4, 8, 16, 24, 32, 40, 48 and 52

The mean changes in CST measured by SD-OCT were globally similar between the treatment groups at the time points provided. Additionally, a decrease is observed in CST in both treatment arms from Week 8 to Week 16. At baseline, the mean CST (SD) was 430 (± 117.46) and 436.2 (± 128.12) µm in Mynzepli and in Eylea group, respectively and -161.8 (± 126.46) and -168.8 (± 116.42) µm in Mynzepli and in Eylea group, respectively at week 24. The LS mean difference (Mynzepli –Eylea) observed at Week 24 was -1.3 µm and 95% CI [-24.1, 21.4] moreover the LS mean difference (Mynzepli –Eylea) observed at Week 52 was -14.8 µm and 95% CI [-37.8, 8.2].

Mean change in CNV from baseline to Week 8, 24 and Week 52.

The changes in CNV were comparable between the treatment groups and the two methods of assessment (FA and color FP) at week 8 and 24. Mean CNV at baseline is described in the baseline data. However, according to the applicant, the mean CNV (SD) at Week 24 was -0.086 (2.9586) and -0.443 (2.6268) mm^2 in Mynzepli and in Eylea group, respectively with FA and -0.082 (2.9664) and -0.414 (2.6508) mm^2 with color FP in Eylea group, respectively. The LS mean difference (Mynzepli –Eylea) observed at Week 24 was 0.35 mm^2 and 95% CI [-0.24, 0.95] with FA and 0.33 mm^2 and 95% CI [-0.27, 0.93] with color FP.

The changes in CNV were comparable between the treatment groups and the two methods of assessment (FA and color FP) at week 52. According to the applicant, the mean CNV (SD) at Week 52 was -2.807 (4.5875) and -3.166 (4.9652) mm^2 in Mynzepli and in Eylea group, respectively with FA and -2.805 (4.5886) and -3.127 (5.0059) mm^2 with color FP in Eylea group, respectively. The LS mean difference (Mynzepli –Eylea) observed at Week 52 was 0.22 mm^2 and 95% CI [-0.87, 1.30] with FA and 0.18 mm^2 and 95% CI [-0.91, 1.28] with color FP.

Absence of intra/subretinal fluid from baseline to Week 4, 8, 16, 24, 32, 40, 48 and 52

The proportion of Subjects without Intra- or Sub-Retinal Fluid on SD-OCT was comparable between treatments groups over time.

At baseline, 45 (22%) and 55 (26.8%) patients presented absence of intraretinal fluid in Mynzepli and Eylea arms, respectively. At 24 weeks, this was observed in 56 patients (36.8%) in Mynzepli arm and 55 patients (39.6%) in Eylea arm. At 52 weeks, this was observed in 74 patients (51.7%) in Mynzepli arm and 61 patients (44.2%) in Eylea arm. The estimated difference in proportion (Mynzepli –Eylea) was 0.03 and 95% CI [-0.03, 0.08]

At baseline, 13 (6.3%) and 12 (5.9%) patients presented absence of subretinal fluid in Mynzepli and Eylea arms, respectively. At 24 weeks, this was observed in 86 patients (47%) in Mynzepli arm and 95 patients (52.5%) in Eylea arm. At 52 weeks, this was observed in 106 patients (61.3%) in Mynzepli arm and 121 patients (68.4%) in Eylea arm. The estimated difference in proportion (Mynzepli –Eylea) was -0.03 and 95% CI [-0.08, 0.02].

The slight decrease in CST from Week 8 to Week 16 is most likely due to the fact that the Week 16 assessment occurred 8 weeks after the last study drug administration, while the assessments at Week 4 and Week 8 were conducted 4 weeks after the previous dose.

The applicant uses mixed model for repeated measures (MMRM) for primary efficacy endpoint change from baseline to Week 8 in BCVA as measured by ETDRS letter score. Secondary efficacy endpoints also include change from baseline in BCVA as measured by ETDRS letter score, but with respect to other weeks (Week 4, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52, respectively). However, statistical analysis to other weeks is based on analysis of covariance model which differs from MMRM by structure of fixed effects and absence of random effect using unstructured covariance structure. The applicant provided requested calculations based on MMRM which extends analysis of primary endpoint to other weeks than only to Week 8. Equivalence of test product Mynzepli to reference product Eylea is investigated with respect to equivalence range (ER) given by (-3.5 letters, 3.5 letters) for difference between Mynzepli and Eylea with respect to primary endpoint. If other visits are taken into account, then equivalence is concluded at Week 4, Week 8, Week 16, Week 24, Week 32 and Week 40, respectively, as 95% CI for difference between Mynzepli and Eylea is fully included within ER. On the other hand, equivalence is not concluded at Week 48 and Week 52, respectively, as 95% CI for difference between Mynzepli and Eylea is not fully included within ER (-3.5 letters, 3.5 letters). More specifically, estimated difference in letters with 95% CI in letters is -1.24 with (-3.76, 1.27) at Week 48 and -0.94 with (-3.54, 1.66) at Week 52, i.e., lower limit of each 95% CI is below -3.5.

The applicant suggests that the study is sufficiently powered to detect assumed treatment effect only with respect to primary endpoint change from baseline to Week 8 in BCVA as measured by ETDRS letter score. Assumptions are not posed for other study visits including Week 48, i.e., Week 4, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52, respectively. Moreover, changes from baseline to other study visits (Week 4, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52, respectively) in BCVA as measured by ETDRS letter score are presented as secondary endpoints with descriptive purpose. In case of descriptive purpose, consistency in results is usually demonstrated if point estimate for difference between Mynzepli and Eylea is within ER (-3.5 letters, 3.5 letters). Point estimate is within ER (-3.5 letters, 3.5 letters) for each study visit. Also, standard deviation increases both for Mynzepli and Eylea beyond Week 8 which can lead to insufficient statistical power (less than 80%) to conclude equivalence with respect to ER (-3.5 letters, 3.5 letters) taking into account that number of patients is formally derived only with respect to change from baseline to Week 8.

The applicant presented recalculation based on “hypothetical estimand strategy”. However, after this recalculation the same situation occurred as in case of calculation based on “treatment policy strategy”. More specifically, equivalence with respect to ER (-3.5 letters, 3.5 letters) is not concluded

at Week 48 as 95% CI for difference between Mynzepli and Eylea is (-3.51 letters, 1.39 letter) and this 95% CI is not fully within ER (-3.5 letters, 3.5 letters). Similar argumentation for Week 48 can be applied also in case of "hypothetical estimand strategy". At first, study is not powered with respect to change from baseline to Week 48. At second, point estimate for difference between Mynzepli and Eylea lies fully within ER (-3.5 letters, 3.5 letters) as results based on other study visits are considered rather as descriptive.

The applicant uses logistic regression model (LRM) for assessment of proportion of patients with gain/loss of certain number of letters (at least 5, at least 10 and at least 15, respectively) from baseline to Week 4, Week 8, Week 16 and Week 24, respectively. Based on Appendix 6. SAS Code For Logistic Regression and Delta Method which can be found in Appendix 16.1.9. Documentation of Statistical Methods, LRM considers logit link function and covariate-adjusted absolute difference between proportions with corresponding 95% confidence interval is calculated by delta method. Query was raised regarding use of LRM with identity link function to evaluate absolute difference between proportions (treatments) instead of consideration of LRM with logit link function and delta method. Reasoning is that LRM with logit link function evaluates relative difference between proportions by odds ratio instead of absolute difference between proportions. However, this query was not properly answered by the applicant as abbreviation LRM was wrongly considered as abbreviation for linear regression model. Thus, query regarding use of LRM with identity link function prevails. The applicant justifies problem with estimation as known limitation of LRM with ILF because ILF is not constrained to produce predictions within close interval <0,1> compared to canonical link function given by logit link function. But at least for 12 available results based on use of LRM with ILF, results are consistent with use of LRM with logit link function combined with delta method.

Overall, the analyses of the primary and secondary efficacy endpoints tend to support the notion of similarity between Mynzepli and the reference product Eylea (aflibercept EU) through 52 Weeks. As a response to the to the D120 LoQ, the applicant provided efficacy and safety data up to 52 weeks. Based on the results submitted, equivalence between Mynzepli and Eylea is not concluded at Week 48 if analysis of covariance (ANCOVA) model for endpoint given by change from baseline to individual study visits in BCVA as measured by ETDRS letter score is considered. Corresponding 95% CI for difference between Mynzepli and Eylea at Week 48 is not fully included within ER (-3.5 letters, 3.5 letters). Moreover, it seems that results based on ANCOVA model are only provided for "treatment policy strategy" where analysis is based on FAS without exclusion of any data for subjects with any pre-specified intercurrent events (ICEs). However, there is also "hypothetical strategy" where analysis is based on FAS with exclusion of subject's data at and after the occurrence of any of pre-specified ICEs. Therefore, The applicant applied the same ICEs as those defined for the primary estimands. Accordingly, subjects' data following the occurrence of any of these ICEs were excluded from the ad hoc analysis of the secondary endpoint, using the same methodology as for the Week 8 primary endpoint analysis. According to the results provided by the applicant the 95% confidence intervals (CIs) for all time points fell within the predefined equivalence margins of [-3.5; 3.5], with one exception: a marginal breach of the lower 95% limit at Week 48 (-3.51). The LS mean difference (Mynzepli – Eylea) observed at this time point, amounting to 1.06 letters, represents the largest difference across all assessed time points. However, as mentioned above, it can be concluded that at Week 48, the change in LS mean BCVA letter score from baseline was comparable between the Mynzepli and Eylea groups.

2.4.7. Conclusions on the clinical efficacy

The efficacy data presented supports biosimilarity between Mynzepli and the reference medicinal product.

2.4.8. Clinical safety

The safety of Mynzepli (as a proposed similar biological medicinal product to Eylea) is supported by AVT06-GL-C01, a single comparative 52-weeks phase III randomized, double-masked, parallel-group, multicenter clinical study (117 study centres, 14 countries). In the two scientific advices given for Mynzepli (DKMA Scientific Advice Meeting, Dec 2020 and EMA/SA/0000063900, Sept 2021), it was agreed that a single efficacy and safety study, AVT06-GL-301, is adequate to demonstrate clinical similarity of Mynzepli and EU-Eylea. Moreover, a separate comparative pharmacokinetic study was considered as not warranted nor useful to support similarity. After intravitreal administration of aflibercept, systemic exposure is expected to be very low and highly variable.

Mynzepli was administered via intravitreal route at a dose of 2 mg every 4 weeks for the first 3 months, followed by 2 mg once every 8 weeks up to Week 48. Last assessment was supposed to be done at Week 56. The last visit of the last subject took place on 20. 9. 2024 (with respect to data included in CSR). On D-120 LoQ, the applicant provided results up to 52-weeks.

Mynzepli is a biosimilar of aflibercept which will be available in two presentations: a 2 mg/0.05 mL single-dose glass vial and a 2 mg/0.05 mL single-dose pre-filled glass syringe. While sing two similar container systems (vial vs vial or PFS vs PFS) would have been the preferred approach, it is recognised that the Mynzepli PFS is still currently under development and that its safety profile should not majorly differ from the known safety profile of the Mynzepli vial, moreover blinding was performed as to ensure that the safety assessments were unbiased. Mynzepli is composed of Polysorbate, sucrose, α,α-trehalose and histidine which use are established in other formulations for intravitreal use. Another component is Poloxamer 188 which is not regarded as a novel nor an excipient generally associated with any theoretical safety concerns; however, its use in intravitreal formulations has not been established.

Regarding the schedule of assessment, it was recommended in the scientific advice that immunogenicity testing at baseline, Week 8, 12, 24 (or 2-3 samples the first 1-4 months) and 52 would be sufficient. In study AVT06-GL-C01, immunogenicity blood samplings were done at baseline, Week 4, 8, 16, 24, and 52 which is acceptable. Additionally, regarding the safety assessment the applicant was advised to add a visit for all subjects at day 1 or 2, and one week after the first injection, and to evaluate safety (and preferably also efficacy) on a monthly basis, at least up to Week 24 (EMA/SA/0000063900, Sept 2021). In study AVT06-GL-C01, AE/SAE/AESI will be reviewed at every scheduled visit (baseline, week 4, 8, 16, 24, 32, 40, 48 and 52) and a safety phone call was performed 3 days (±1 day) after the study treatment administration. The applicant did not follow the advice regarding the addition of a visit at week 12 and 20 to follow a monthly evaluation up to at least week 24, although this would have been preferable, this is still considered as acceptable.

2.4.8.1. Patient exposure

A total of 413 participants were included in the study (randomized as follows: Mynzepli – 206, Eylea – 207). The safety analysis set (patients) included 410 participants (205 participants each in Mynzepli and Eylea treatment arms) who receive at least 1 dose of study treatment and consisted of male and female participant's ≥50 years of age with neovascular (wet) AMD with a 1:1 ratio of patients treated with 2 mg (0.05 mL) IVT Mynzepli and 2 mg (0.05 mL) IVT EU-Eylea treatment arms which is acceptable for the determination of the basic safety profile.

Table 30: Study Treatment Exposure up to Week 52 (Safety Analysis Set)

Description	Statistic	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
Overall duration of exposure (weeks)	N	205	205	410
	Mean (SD)	46.523 (7.0090)	45.522 (9.3082)	46.023 (8.2444)
	Median	48.143	48.143	48.143
	Min, Max	8.14, 53.14	0.14, 52.29	0.14, 53.14
Total dose (mg)	N	205	205	410
	Mean (SD)	15.5 (1.79)	15.2 (2.54)	15.3 (2.20)
	Median	16.0	16.0	16.0
	Min, Max	6, 16	2, 16	2, 16
Number of injections received	8	181 (88.3)	176 (85.9)	357 (87.1)
	7	14 (6.8)	11 (5.4)	25 (6.1)
	6	1 (0.5)	5 (2.4)	6 (1.5)
	5	3 (1.5)	2 (1.0)	5 (1.2)
	4	2 (1.0)	2 (1.0)	4 (1.0)
	3	4 (2.0)	5 (2.4)	9 (2.2)
	2	0	3 (1.5)	3 (0.7)
	1	0	1 (0.5)	1 (0.2)
	0	0	0	0
Number of injections missed	0	196 (95.6)	191 (93.2)	387 (94.4)
	1	9 (4.4)	10 (4.9)	19 (4.6)
	2	0	3 (1.5)	3 (0.7)
	3	0	1 (0.5)	1 (0.2)
	4	0	0	0
	5	0	0	0
	6	0	0	0
	7	0	0	0
	8	0	0	0
Compliance to study treatment (%)	N	205	205	410
	Mean (SD)	99.45 (2.567)	98.68 (5.477)	99.07 (4.289)
	Median	100.00	100.00	100.00
	Min, Max	87.5, 100.0	62.5, 100.0	62.5, 100.0

n: Number of subjects, SD: Standard deviation.
Dose value of 2 mg: 0.05mL
Total dose is a maximum of 10 mg (2 mg per injection, with 5 injections in total)
Duration of exposure (weeks): (Date of last study treatment injection - Date of first study treatment injection + 1) / 7.
The number of missed injections is calculated as the expected number of injections minus the number of injections received. Expected number may differ across subjects depending on when they stop the study - there is a maximum of 5 injections.
Compliance to study treatment: (Number of injections received/expected number of injections) x 100.
Percentages are calculated out of the number of subjects included in the safety analysis set per treatment group.

An 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.

The number of doses and the duration of exposure were comparable. Up to 52 weeks, patients in study received a median total number of 8 injections for 88.3% in Mynzepli arm and 85.9% in EU-Eylea arm. The overall duration of exposure is of 46.523 weeks in Mynzepli and 45.22 weeks in EU-Eylea arms. The mean total dose received is of 15.5 mg in Mynzepli arm and 15.2 mg in EU-Eylea. The Compliance to study treatment was well observed with a mean around 99% in both treatment arms (99.45% in Mynzepli and 98.68% in Eylea).

There are no safety concerns regarding to patient exposure at the moment. Demographic and baseline characteristics were comparable between both treatment arms although discussion were further required (see Clinical Efficacy section for comments).

2.4.8.2. Adverse events

2.4.8.2.1. Overall TEAEs

Overview of TEAEs up to Week 24 and 52 have been presented. Up to week 52, 63.4% of the patients experienced 762 TEAEs. Overall, a total of 47.8% and 68.8% of the patients in Mynzepli and 46.3% and 58.0% of the patients in EU-Eylea experienced at least one adverse events up to week 24 and 52 respectively. TEAEs were reported in comparable incidences between Mynzepli arm (46.3%, 95 participants up to week 24 and 67.8%, 139 participants up to week 52) and EU-Eylea arm (43.4%, 89 participants up to week 24 and 56.1%, 115 participants up to week 52). Ocular TEAEs in the study eye were reported in comparable incidence between both treatment arms up to week 52 (16.1%, 33 participants in Mynzepli and 15.6%, 32 participants in EU-Eylea up to week 24 and 24.9%, 51 participants in Mynzepli and 21.5%, 44 participants in EU-Eylea) while ocular AE in the fellow eye were slightly more reported in Mynzepli arm up to week 24 (11.7% vs 7.8% in EU-Eylea arm) and week 52 (20.0% vs 14.6% in EU-Eylea arm). Non-ocular AE were reported in comparable proportions between treatment arms (33.7% in Mynzepli and 32.2% in EU-Eylea up to week 24 and 52.7% in Mynzepli and 45.4% in EU-Eylea up to week 52).

TEAE assessed as related to study medication by the investigator were few and proportions were comparable between treatment arms up to week 24 (3.4%, 7 subjects experienced 10 TEAEs in Mynzepli and 2.4%, 5 subjects experienced 6 TEAEs in EU-Eylea) and up to week 52 (4.9%, 10 subjects experienced 14 TEAEs in Mynzepli and 3.4%, 7 subjects experienced 11 TEAEs in EU-Eylea). Most of the subjects experienced treatment-related ocular TEAEs and 1 subject in the Eylea group (ID 150201) had 2 non-ocular TEAEs (Alanine aminotransferase increased and Gamma-glutamyl transferase increased) considered possibly related to Eylea (see section 3.3.7.3 Treatment-Related TEAEs by SOC and PT).

The severity of each AE was recorded as mild, moderate, or severe. TEAEs were mainly mild to moderate (33.7% (AVT-06) vs 28.8% (EU-Eylea) and 10.7% (AVT-06) vs 11.2% (EU-Eylea) up to week 24 and 46.3% (AVT-06) vs 33.0% (EU-Eylea) and 19.0% (AVT-06) vs 17.1% (EU-Eylea) up to week 52). Severe TEAE were reported in low and comparable proportions (2.0% in Mynzepli and 2.9% in EU-Eylea up to week 24 and 2.0% in Mynzepli and 4.9% in EU-Eylea up to week 52).

Two deaths were reported in the EU-Eylea treatment arm and assessed as not related to study treatment. Serious TEAEs were more reported in the EU-Eylea arm (4.4% vs 1.0% in Mynzepli up to week 24 and 8.3% vs 3.4% in AVT-06) and none were assessed as related to study treatment. TEAE leading to study treatment discontinuation or study discontinuation were low and comparable between treatment arms up to week 24 (respectively 1.0% in Mynzepli and 1.5% and 1.0% in EU-Eylea) and week 52 (respectively 2.0% and 1.5% in Mynzepli and 2.4 % and 2.0% in EU-Eylea). One TEAE leading to study discontinuation and one TEAE leading to study treatment discontinuation were assessed as related to study treatment in Mynzepli arm up to week 52. Treatment emergent AESI were comparable (4.4% and 6.8% Mynzepli and 4.9% and 7.3% in EU-Eylea up to week 24 and week 52 respectively) and 2.0% and 1.0% respectively were assessed as study treatment related in Mynzepli and EU-Eylea treatment arm up to week 24 (2.4% in AVT-06 and 1.5% in EU-Eylea up to week 52).

Table 31: Overview of Adverse Events up to Week 52 (Safety Analysis Set)

	AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
System Organ Class Preferred Term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**M**
Any adverse events	141 (68.8)	371	119 (58.0)	391	260 (63.4)	762
Any TEAE	139 (67.8)	349	115 (56.1)	376	254 (62.0)	725
Ocular AE in the study eye	51 (24.9)	76	44 (21.5)	71	95 (23.2)	147
Ocular AE in the fellow eye	41 (20.0)	51	30 (14.6)	33	71 (17.3)	84
Non-ocular AE	108 (52.7)	222	93 (45.4)	272	201 (49.0)	494
TEAE related to study treatment	10 (4.9)	14	7 (3.4)	11	17 (4.1)	25
Maximum severity of TEAE						
Mild	95 (46.3)	277	68 (33.2)	259	163 (39.8)	536
Moderate	39 (19.0)	65	35 (17.1)	100	74 (18.0)	165
Severe	4 (2.0)	4	10 (4.9)	15	14 (3.4)	19
Life-threatening	0	0	0	0	0	0
Death	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
TEAEs with severe severity or worse	5 (2.4)	7	12 (5.9)	17	17 (4.1)	24
TEAEs with severe severity or worse and related to study treatment	1 (0.5)	1	0	0	1 (0.2)	1
Any serious TEAEs	7 (3.4)	10	17 (8.3)	24	24 (5.9)	34
Any serious TEAEs related to study treatment	0	0	0	0	0	0
TEAEs leading to discontinuation of study treatment	4 (2.0)	4	5 (2.4)	7	9 (2.2)	11
TEAEs leading to discontinuation of study treatment and related to study treatment	1 (0.5)	1	0	0	1 (0.2)	1
TEAEs leading to discontinuation of study	3 (1.5)	3	4 (2.0)	4	7 (1.7)	7
TEAEs leading to discontinuation of study and related to study treatment	1 (0.5)	1	0	0	1 (0.2)	1
TEAEs leading to death	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
TEAEs leading to death and related to study drug	0	0	0	0	0	0
Any treatment emergent AESIs	14 (6.8)	17	15 (7.3)	19	29 (7.1)	36
Any related treatment emergent AESIs	5 (2.4)	5	3 (1.5)	4	8 (2.0)	9

AE: Adverse Event, AESI: Adverse Event of Special Interest, m: Number of events, n: Number of participants experiencing the event, TEAE: Treatment-Emergent AEs.
Note: Percentages are based on the total number of participants in the Safety Analysis Set per treatment group.
Adverse Events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 27.0.
Participants with multiple occurrences of TEAEs will have the TEAE with the worst severity included in this summary.
Related = "Certainly Related", "Probably Related", "Possibly Related", "Unknown"; Not Related = "Unlikely to be Related", "Unrelated".
Subject IDs: 110905 and 210907 had an AE leading to discontinuation of study treatment and discontinuation of study, however reason for discontinuation on the End of Treatment Period and End of Study CRF pages is Death.

2.4.8.2.2. Ocular Adverse Events in Study Eye

Ocular TEAEs in the study eye were reported in comparable proportions between Mynzepli and EU-Eylea arms (16.1% and 15.6% up to week 24 and 24.9% vs 21.5% up to week 52). Ocular TEAEs in the study eye were mainly mild to moderate (12.2% and 2.9% in Mynzepli arm and 10.7% and 4.9% in EU-Eylea arm up to week 24 and 19.5% and 4.4% in Mynzepli arm and 15.1% and 6.3% in EU-Eylea arm up to week 52). Ocular TEAEs in the study eye assessed as treatment related were slightly higher in Mynzepli arm (3.4% vs 2.0% in EU-Eylea arm up to week 24 and 4.9% vs 2.9% in EU-Eylea arm up to week 52). Severe ocular TEAEs in the study eye were reported in 2 patients (1.0%) in Mynzepli arm up to week 52. One severe ocular TEAEs in the study eye and assessed as related to study drug was reported in Mynzepli arm. No serious ocular TEAEs in the study eye were reported up to week 52. One ocular TEAE in the study eye led to study treatment discontinuation in Mynzepli arm (assessed as treatment related) and one ocular TEAE in the study eye led to study discontinuation in both Mynzepli and EU-Eylea arms. No ocular TEAEs in the study eye led to patient's death. Treatment emergent AESI in the study eye occurred in comparable proportions (3.4% in both Mynzepli and EU-Eylea arm up to week 24 and 3.9% in AVT-06 and 4.4% in EU-Eylea arm up to week 52) and 2.0% and 1.0% respectively were assessed as treatment related in Mynzepli and in EU-Eylea arms up to week 24 (2.4% and 1.5% up to week 52).

Table 32: Overview of Ocular Adverse Events in Study Eye up to Week 52 (Safety Analysis Set)

	AVT06 (N=205)		**Eylea (N=205)**		**Total (N=410)**	
System Organ Class Preferred Term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**M**
Any adverse events	51 (24.9)	76	44 (21.5)	71	95 (23.2)	147
Any TEAE	51 (24.9)	76	44 (21.5)	71	95 (23.2)	147
TEAE related to study treatment	10 (4.9)	14	6 (2.9)	8	16 (3.9)	22
Maximum severity of TEAE						
Mild	40 (19.5)	62	31 (15.1)	55	71 (17.3)	117
Moderate	9 (4.4)	12	13 (6.3)	16	22 (5.4)	28
Severe	2 (1.0)	2	0	0	2 (0.5)	2
Life-threatening	0	0	0	0	0	0
Death	0	0	0	0	0	0
TEAEs with severe severity or worse	2 (1.0)	2	0	0	2 (0.5)	2
TEAEs with severe severity or worse and related to study treatment	1 (0.5)	1	0	0	1 (0.2)	1
Any serious TEAEs	0	0	0	0	0	0
Any serious TEAEs related to study treatment	0	0	0	0	0	0
TEAEs leading to discontinuation of study treatment	1 (0.5)	1	2 (1.0)	3	3 (0.7)	4
TEAEs leading to discontinuation of study treatment and related to study treatment	1 (0.5)	1	0	0	1 (0.2)	1
TEAEs leading to discontinuation of study	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
TEAEs leading to discontinuation of study and related to study treatment	1 (0.5)	1	0	0	1 (0.2)	1
TEAEs leading to death	0	0	0	0	0	0
TEAEs leading to death and related to study drug	0	0	0	0	0	0
Any treatment emergent AESIs	8 (3.9)	9	9 (4.4)	11	17 (4.1)	20
Any related treatment emergent AESIs	5 (2.4)	5	3 (1.5)	4	8 (2.0)	9

2.4.8.2.3. Ocular Adverse Events in Non-Study Eye and Non-Ocular Adverse Events

Ocular AEs in the fellow eye occurred in slightly higher proportion in the Mynzepli arm (11.7% vs 7.8% in EU-Eylea arm up to week 24). Non-ocular AEs were reported in comparable proportions between treatment arms (33.7% in Mynzepli arm and 32.2% in EU-Eylea arm) up to week 24. In the D120 LoQ, the applicant provided appendix 9 "Overview of Ocular Adverse Events in Fellow Eye up to Week 52" and appendix 10 "Overview of Non-Ocular Adverse Events up to Week 52". Overall, up to 52 weeks, a slightly higher proportions of patients presented TEAEs in the fellow eye in the AVT-06 arm (20.0%) compared to Eylea (14.6%). TEAEs were majorly mild to moderate in severity. One serious TEAE occurred in AVT-06 compared to none in Eylea. Non-Ocular TEAEs were also more reported in AVT-06 (52.7% vs 45.4% in Eylea). Non-Ocular TEAEs were majorly mild to moderate in severity. Severe non-ocular TEAEs were more reported in Eylea arm (5.9% vs 1.5%). Serious non-ocular TEAEs were also more reported in Eylea arm (8.3% vs 2.9%). None were assessed as related to study treatment. Non-Ocular TEAEs leading to study discontinuation were reported in comparable proportions (1.5% in AVT-06 and 1.0% in Eylea).

Table 33: Overview of Ocular Adverse Events in Fellow Eye and Non-Ocular Adverse Events up to Week 52 (Safety Analysis Set)

	AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
	n (%)	m	n (%)	m	n (%)	M
Any adverse events	127 (62.0)	295	110 (53.7)	320	237 (57.8)	615
Any TEAE	124 (60.5)	273	106 (51.7)	305	230 (56.1)	578
TEAE related to study treatment	0	0	1 (0.5)	3	1 (0.2)	3
Maximum severity of TEAE						
Mild	86 (42.0)	215	65 (31.7)	204	151 (36.8)	419
Moderate	35 (17.1)	53	29 (14.1)	84	64 (15.6)	137
Severe	2 (1.0)	2	10 (4.9)	15	12 (2.9)	17
Life-threatening	0	0	0	0	0	0
Death	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
TEAEs with severe severity or worse	3 (1.5)	5	12 (5.9)	17	15 (3.7)	22
TEAEs with severe severity or worse and related to study treatment	0	0	0	0	0	0
Any serious TEAEs	7 (3.4)	10	17 (8.3)	24	24 (5.9)	34
Any serious TEAEs related to study treatment	0	0	0	0	0	0
TEAEs leading to discontinuation of study treatment	3 (1.5)	3	2 (1.0)	2	5 (1.2)	5
TEAEs leading to discontinuation of study treatment and related to study treatment	0	0	0	0	0	0
TEAEs leading to discontinuation of study	2 (1.0)	2	3 (1.5)	3	5 (1.2)	5
TEAEs leading to discontinuation of study and related to study treatment	0	0	0	0	0	0
TEAEs leading to death	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
TEAEs leading to death and related to study drug	0	0	0	0	0	0
Any treatment-emergent AESIs	7 (3.4)	8	6 (2.9)	8	13 (3.2)	16
Any related treatment-emergent AESIs	0	0	0	0	0	0

2.4.8.2.4. TEAEs Occurring in >5% and of the Participants by SOC and PT

The risk adjusted incidence rate of TEAEs (number of subjects with events per 100 total person-years at risk calculated by Number of subjects with TEAE/Total PY)*100) up to Week 24 in the Mynzepli group was higher (139.5%) compared to the Eylea group (128.5%). Similarly, up to week 52, the risk-adjusted incidence rate of TEAEs in the Mynzepli group was 129.8% and in the Eylea group was 102.1%.

The most reported SOC were Eye disorders (20.0% in Mynzepli arm and 18.5% in EU-Eylea arm up to week 24 and 31.7% vs 26.8% up to week 52) and Infections and infestations (higher in Mynzepli with 14.6% vs 10.7% in EU-Eylea arm and 22.4% vs 20.5% up to week 52). The most reported PT (>5% of the participants) was nAMD in the fellow eye (5.9 in Mynzepli arm and 6.8% in EU-Eylea arm up to week 24 and 10.7% vs 10.2% up to week 52) and nasopharyngitis (higher in Mynzepli with 6.8% vs 2.0% in EU-Eylea arm up to week 24 and 9.3% vs 3.4% up to week 52).

Table 34: Incidence of TEAEs Occurring in ⩾5% of Participants up to Week 52 by SOC and PT (Safety Analysis Set)

	AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
System Organ Class Preferred Term	**n (%)**	**M**	**n (%)**	**m**	**n (%)**	**M**
Subjects with at least one TEAE	139 (67.8)	349	115 (56.1)	376	254 (62.0)	725
Ocular TEAEs						
Subjects with at least one ocular TEAE	71 (34.6)	127	61 (29.8)	104	132 (32.2)	231
Eye disorders	65 (31.7)	107	55 (26.8)	92	120 (29.3)	199
Neovascular age-related macular degeneration	22 (10.7)	23	21 (10.2)	22	43 (10.5)	45
Non-ocular TEAEs						
Subjects with at least one non-ocular TEAE	108 (52.7)	222	93 (45.4)	272	201 (49.0)	494
Infections and infestations	46 (22.4)	61	42 (20.5)	57	88 (21.5)	118
Nasopharyngitis	19 (9.3)	24	7 (3.4)	8	26 (6.3)	32

Ocular TEAEs (study eye and fellow eye) occurring in more than 1% of the participants were reported in comparable proportions between treatment arms up to week 24 and week 52. Most reported PT consisted of Conjunctival haemorrhage (2.9% Mynzepli arm vs 2.0% EU-Eylea arm up to week 24 and 3.9% Mynzepli arm vs 2.4% EU-Eylea arm up to week 52), Retinal pigment epithelial tear (2.4% Mynzepli arm vs 1.5% EU-Eylea arm up to week 24 and 2.4% Mynzepli arm vs 2.0 % EU-Eylea arm up to week 52), vitreous floaters (2.4% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 2.9% Mynzepli arm vs 1.5% EU-Eylea arm up to week 52), Visual acuity reduced (1.0% Mynzepli arm vs 1.5% EU-Eylea arm up to week 24 and week 52), Eye pain (1.0% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 1.0% Mynzepli arm vs 1.5% EU-Eylea arm up to week 52), Cataract (0.5% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 2.0% Mynzepli arm vs 2.4 % EU-Eylea arm up to week 52), Punctuate keratitis (1.0% Mynzepli arm vs 0.5% EU-Eylea arm up to week 24 and 52), Retinal haemorrhage (0.5% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 1.0% Mynzepli arm vs 1.0% EU-Eylea up to week 52), Conjunctival hyperaemia (1.0 % Mynzepli arm vs 0% EU-Eylea arm up to week 24 and 52), Macula Scar (1.0% Mynzepli arm vs 0% EU-Eylea arm up to week 24 and 52), Conjunctivis viral (1.0% Mynzepli arm vs 0% EU-Eylea arm up to week 24 and 52) and IOP increased (0.5% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 52). These events, except macular scar and conjunctivitis viral are all events reported with aflibercept. The risk adjusted rate for most reported ocular TEAEs up to week 24 were neovascular age related macular degeneration (Mynzepli: 12.9%; Eylea: 15.5%), conjunctival haemorrhage (Mynzepli: 6.4%; Eylea: 4.3%), retinal pigment epithelial tear and vitreous floaters (Mynzepli: 5.3%; Eylea: 3.2%).

The applicant provided appendix 11 "Incidence of Treatment-Emergent Adverse Events in Study Eye Occurring in >=1% of Subjects up to Week 52 by System Organ Class and Preferred Term" and appendix 12 "Incidence of Treatment-Emergent Adverse Events in Fellow Eye Occurring in >=1% of Subjects up to Week 52 by System Organ Class and Preferred Term". For the fellow eye, the most reported ocular TEAEs was nAMD which was reported in comparable proportions between treatment arms (10.2% AVT-06 vs 9.8% in Eylea). TEAEs in the SOC eye disorders occurring in >=1% of Subjects were reported in comparable proportions between treatment arms. For the study eye, the most reported ocular TEAE were Conjunctival haemorrhage (Mynzepli: 3.9%; Eylea: 2.0%), Cataract (Mynzepli: 2.0%; Eylea: 2.4%), Retinal pigment epithelial tear (Mynzepli: 2.4%; Eylea: 2.0%),

Vitreous floaters (Mynzepli: 2.4%; Eylea: 1.5%). Ocular TEAEs occurring in >=1% of Subjects up to Week 52 in the study eye were reported in comparable proportions between treatment arms.

Non-ocular TEAEs occurring in more than 1% of the participants were consistent with the study population and consisted for the most reported of Headache, Osteoarthritis, Back pain, urinary tract infection, COVID-19 and Rhinitis. All events reported in more than 1% of the population were observed in comparable proportions between treatment arms except nasopharyngitis which was more reported for Mynzepli (Mynzepli: 6.8%; Eylea: 2.0% up to week 24 and 9.3% vs 3.4% up to week 52). Nasopharyngitis was not assessed as related to the study treatment in any of the subjects. The risk adjusted ratio for most reported non-ocular TEAEs were nasopharyngitis (Mynzepli: 15.3%; Eylea: 4.3%), headache (Mynzepli: 8.6%; Eylea: 6.5%) and osteoarthritis (Mynzepli: 0.0%; Eylea: 5.4%). It is acknowledged that nasopharyngitis is a common ailment in elder population, all cases were mild to moderate in severity, resolved and none were assessed as related to study drug.

Table 35: Incidence of TEAEs Occurring in ⩾1% of Participants up to Week 52 by SOC and PT (Safety Analysis Set)

	AVT06 (N=205)		**Eylea (N=205)**		**Total (N=410)**	
System Organ Class Preferred Term	**n (%)**	**M**	**n (%)**	**M**	**n (%)**	**m**
Subjects with at least one TEAE	139 (67.8)	349	115 (56.1)	376	254 (62.0)	725
Ocular TEAEs						
Subjects with at least one ocular TEAE	71 (34.6)	127	61 (29.8)	104	132 (32.2)	231
Eye disorders	65 (31.7)	107	55 (26.8)	92	120 (29.3)	199
Neovascular age-related macular degeneration	22 (10.7)	23	21 (10.2)	22	43 (10.5)	45
Conjunctival haemorrhage	8 (3.9)	8	5 (2.4)	6	13 (3.2)	14
Cataract	4 (2.0)	5	5 (2.4)	7	9 (2.2)	12
Retinal pigment epithelial tear	5 (2.4)	5	4 (2.0)	4	9 (2.2)	9
Vitreous floaters	6 (2.9)	6	3 (1.5)	4	9 (2.2)	10
Eye pain	2 (1.0)	3	3 (1.5)	5	5 (1.2)	8
Visual acuity reduced	2 (1.0)	2	3 (1.5)	3	5 (1.2)	5
Dry eye	4 (2.0)	4	0	0	4 (1.0)	4
Eye irritation	2 (1.0)	3	2 (1.0)	2	4 (1.0)	5
Retinal haemorrhage	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Visual impairment	1 (0.5)	1	3 (1.5)	3	4 (1.0)	4
Cataract nuclear	2 (1.0)	3	1 (0.5)	2	3 (0.7)	5
Choroidal neovascularisation	2 (1.0)	2	1 (0.5)	1	3 (0.7)	3
Epiretinal membrane	2 (1.0)	2	1 (0.5)	1	3 (0.7)	3
Posterior capsule opacification	2 (1.0)	3	1 (0.5)	1	3 (0.7)	4
Punctate keratitis	2 (1.0)	2	1 (0.5)	7	3 (0.7)	9
Vision blurred	2 (1.0)	2	1 (0.5)	1	3 (0.7)	3
Conjunctival hyperaemia	2 (1.0)	4	0	0	2 (0.5)	4
Dry age-related macular degeneration	2 (1.0)	2	0	0	2 (0.5)	2
Iridocyclitis	0	0	2 (1.0)	3	2 (0.5)	3
Lacrimation increased	2 (1.0)	3	0	0	2 (0.5)	3
Macular scar	2 (1.0)	2	0	0	2 (0.5)	2
Infections and infestations	9 (4.4)	15	2 (1.0)	2	11 (2.7)	17
Conjunctivitis	4 (2.0)	4	0	0	4 (1.0)	4
Conjunctivitis viral	2 (1.0)	4	0	0	2 (0.5)	4
General disorders and administration site conditions	3 (1.5)	3	5 (2.4)	5	8 (2.0)	8
Injection site erythema	0	0	2 (1.0)	2	2 (0.5)	2
Investigations	1 (0.5)	1	2 (1.0)	3	3 (0.7)	4

Intraocular pressure increased	1 (0.5)	1	2 (1.0)	3	3 (0.7)	4
Non-ocular TEAEs						
Subjects with at least one non-ocular TEAE	108 (52.7)	222	93 (45.4)	272	201 (49.0)	494
Infections and infestations	46 (22.4)	61	42 (20.5)	57	88 (21.5)	118
Nasopharyngitis	19 (9.3)	24	7 (3.4)	8	26 (6.3)	32
Urinary tract infection	4 (2.0)	5	7 (3.4)	9	11 (2.7)	14
COVID-19	6 (2.9)	6	4 (2.0)	4	10 (2.4)	10
Rhinitis	4 (2.0)	4	4 (2.0)	4	8 (2.0)	8
Pneumonia	4 (2.0)	4	2 (1.0)	2	6 (1.5)	6
Upper respiratory tract infection	0	0	5 (2.4)	6	5 (1.2)	6
Pharyngitis	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Asymptomatic bacteriuria	2 (1.0)	2	1 (0.5)	1	3 (0.7)	3
Gingivitis	1 (0.5)	1	2 (1.0)	2	3 (0.7)	3
Influenza	1 (0.5)	1	2 (1.0)	2	3 (0.7)	3
Cystitis	0	0	2 (1.0)	2	2 (0.5)	2
Herpes zoster	2 (1.0)	2	0	0	2 (0.5)	2
Musculoskeletal and connective tissue disorders	17 (8.3)	20	21 (10.2)	35	38 (9.3)	55
Back pain	8 (3.9)	10	4 (2.0)	4	12 (2.9)	14
Osteoarthritis	1 (0.5)	1	6 (2.9)	8	7 (1.7)	9
Arthralgia	3 (1.5)	3	3 (1.5)	3	6 (1.5)	6
Intervertebral disc disorder	0	0	2 (1.0)	2	2 (0.5)	2
Lumbar spinal stenosis	2 (1.0)	2	0	0	2 (0.5)	2
Osteoporosis	0	0	2 (1.0)	2	2 (0.5)	2
Spinal osteoarthritis	0	0	2 (1.0)	2	2 (0.5)	2
Nervous system disorders	22 (10.7)	23	15 (7.3)	24	37 (9.0)	47
Headache	10 (4.9)	11	6 (2.9)	11	16 (3.9)	22
Carpal tunnel syndrome	4 (2.0)	4	0	0	4 (1.0)	4
Lumbar radiculopathy	1 (0.5)	1	3 (1.5)	3	4 (1.0)	4
Gastrointestinal disorders	15 (7.3)	16	13 (6.3)	18	28 (6.8)	34
Diarrhoea	3 (1.5)	3	4 (2.0)	4	7 (1.7)	7
Gastritis	1 (0.5)	2	2 (1.0)	2	3 (0.7)	4
Cardiac disorders	12 (5.9)	12	9 (4.4)	12	21 (5.1)	24
Atrial fibrillation	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Cardiac failure	2 (1.0)	2	1 (0.5)	2	3 (0.7)	4
Hypertensive heart disease	3 (1.5)	3	0	0	3 (0.7)	3
Respiratory, thoracic and mediastinal disorders	7 (3.4)	7	12 (5.9)	17	19 (4.6)	24
Cough	3 (1.5)	3	2 (1.0)	2	5 (1.2)	5
Rhinitis allergic	1 (0.5)	1	3 (1.5)	3	4 (1.0)	4
Rhinorrhoea	1 (0.5)	1	2 (1.0)	2	3 (0.7)	3
Chronic obstructive pulmonary disease	0	0	2 (1.0)	3	2 (0.5)	3
Investigations	7 (3.4)	8	11 (5.4)	29	18 (4.4)	37
Gamma-glutamyltransferase increased	2 (1.0)	2	4 (2.0)	4	6 (1.5)	6
Blood pressure increased	1 (0.5)	1	3 (1.5)	4	4 (1.0)	5
Alanine aminotransferase increased	0	0	2 (1.0)	4	2 (0.5)	4
Blood alkaline phosphatase increased	0	0	2 (1.0)	2	2 (0.5)	2
Blood creatinine increased	0	0	2 (1.0)	2	2 (0.5)	2
Metabolism and nutrition disorders	9 (4.4)	11	7 (3.4)	10	16 (3.9)	21
Type 2 diabetes mellitus	1 (0.5)	1	3 (1.5)	3	4 (1.0)	4
Dyslipidaemia	0	0	2 (1.0)	2	2 (0.5)	2
Hyperkalaemia	2 (1.0)	2	0	0	2 (0.5)	2
Renal and urinary disorders	11 (5.4)	13	5 (2.4)	8	16 (3.9)	21

Renal cyst	2 (1.0)	2	3 (1.5)	3	5 (1.2)	5
Haematuria	2 (1.0)	2	1 (0.5)	1	3 (0.7)	3
Vascular disorders	9 (4.4)	9	7 (3.4)	8	16 (3.9)	17
Hypertension	6 (2.9)	6	3 (1.5)	3	9 (2.2)	9
Ear and labyrinth disorders	7 (3.4)	8	5 (2.4)	8	12 (2.9)	16
Vertigo	5 (2.4)	5	3 (1.5)	5	8 (2.0)	10
Deafness neurosensory	2 (1.0)	2	0	0	2 (0.5)	2
General disorders and administration site conditions	9 (4.4)	10	2 (1.0)	2	11 (2.7)	12
Pyrexia	6 (2.9)	6	0	0	6 (1.5)	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.0)	2	7 (3.4)	11	9 (2.2)	13
Basal cell carcinoma	0	0	2 (1.0)	2	2 (0.5)	2

m: Number of events, n: Number of subjects experiencing the event, PT: Preferred Term, SOC: System Organ Class, TEAE: Treatment-Emergent Adverse Event.
Adverse Events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 27.0.
Percentages are based on the total number of subjects in the Safety Analysis Set per treatment group. Subjects with more than one event within a SOC or PT are counted only once for that SOC or PT.

2.4.8.2.5. TEAE by Maximum Severity Grade by SOC and PT

TEAEs by maximum severity grade were presented in further details by SOC and PT in Table 36. The applicant provided appendix 13 "Incidence of Treatment-Emergent Adverse Events in Study Eye up to Week 52 by Maximum Severity Grade by System Organ Class and Preferred Term" and appendix 14 "Incidence of Treatment-Emergent Adverse Events in Fellow Eye up to Week 52 by Maximum Severity Grade by System Organ Class and Preferred Term".

Overall, TEAEs were mainly mild (31.2% up to week 24 and 39.8% up to week 52) to moderate (11.0% up to week 24 and 18.0% up to week 52) in severity with a higher proportion of mild severity in Mynzepli arm (33.7% vs 28.8% in EU-Eylea arm up to week 24 and 46.3% vs 32.2% up to week 52). Severe TEAE were seen in low proportions in both treatment arm (2.0% in Mynzepli arm and 2.9% in EU-Eylea arm up to week 24 and 2.0% in Mynzepli arm and 4.9% in EU-Eylea arm up to week 52). Regarding ocular TEAEs, up to week 24 for the SOC Eye disorders, events were mild to moderate with comparable proportions and two severe events (visual acuity reduced and retinal haemorrhage) were reported in Mynzepli arm compared to none in EU-Eylea arm.

Regarding non-ocular TEAEs, severe events were low and consisted up to week 52 of:
- 2 events in AVT-06 (2 patients in total): Pneumonia and Back pain;
- 7 events in EU-Eylea arm (6 patients in total): Lumbar radiculopathy, Ischaemic stroke, Osteoarthritis, Intestinal obstruction, Acute pulmonary oedema, Cardiac failure, and Superficial vein thrombosis. One death occurred up to week 24 (rib fracture) in EU-Eylea arm.
Up to week 52, 8 additional non-ocular TEAEs were reported in 4 patients in EU-Eylea arm: Lower limb fracture, Syncope, Acute respiratory failure, Pulmonary oedema, Superficial vein thrombosis, Viral sepsis, Endometrial cancer, and Ovarian cyst. One additional death was reported in EU-Eylea arm (Colon cancer).

Table 36: Incidence of TEAEs up to Week 52 Occurring in ≥5% of Participants by Maximum Severity Grade by SOC and PT (Safety Analysis Set)

		AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
System Organ Class Preferred Term	**Toxicity Grade**	**n (%)**	**M**	**n (%)**	**m**	**n (%)**	**M**
Subjects with at least one TEAE	Mild	95 (46.3)	277	68 (33.2)	259	163 (39.8)	536
	Moderate	39 (19.0)	65	35 (17.1)	100	74 (18.0)	165
	Severe	4 (2.0)	4	10 (4.9)	15	14 (3.4)	19
	Life-threatening	0	0	0	0	0	0
	Death	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
Eye disorders	Mild	47 (22.9)	85	39 (19.0)	70	86 (21.0)	155
	Moderate	16 (7.8)	20	16 (7.8)	22	32 (7.8)	42
	Severe	2 (1.0)	2	0	0	2 (0.5)	2
	Life-threatening	0	0	0	0	0	0
	Death	0	0	0	0	0	0
Neovascular age-related macular degeneration	Mild	14 (6.8)	15	13 (6.3)	14	27 (6.6)	29
	Moderate	8 (3.9)	8	8 (3.9)	8	16 (3.9)	16
	Severe	0	0	0	0	0	0
	Life-threatening	0	0	0	0	0	0
	Death	0	0	0	0	0	0

m: Number of events, n: Number of subjects experiencing the event, PT: Preferred Term, SOC: System Organ Class, TEAE: Treatment-Emergent Adverse Event.
Percentages are based on the total number of subjects in the Safety Analysis Set per treatment group.
AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 27.0
Subjects with more than one event within a SOC or PT are counted only once for that SOC or PT for the worst severity.

For treatment related TEAEs (section 3.3.7.3 below) up to week 24, 6 subjects had 10 mild TEAEs (Mynzepli: 4 subjects and 7 TEAEs; Eylea: 2 subjects and 3 TEAEs), 5 subjects had 5 moderate TEAEs (Mynzepli: 2 subjects and 2 TEAEs; Eylea: 3 subjects and 3 TEAEs), and 1 subject in the Mynzepli group had a severe TEAE.

Up to week 52, out of 17 subjects experiencing treatment-related TEAEs, 10 subjects had 17 mild TEAEs (Mynzepli: 6 subjects and 10 TEAEs; Eylea: 4 subjects and 7 TEAEs), 6 subjects had 7 moderate TEAEs (Mynzepli: 3 subjects and 3 TEAEs; Eylea: 3 subjects and 4 TEAEs), and 1 subject in the Mynzepli group had a severe TEAE (retinal haemorrhage).

2.4.8.3. Treatment-Related TEAEs by SOC and PT

Up to week 24, comparable incidences of treatment related TEAEs and treatment related ocular TEAEs were reported between Mynzepli and EU-Eylea (3.4% vs 2.4% and 3.4% vs 2.0%, respectively). Up to week 24, these events consisted of:

- In Mynzepli: retinal pigment epithelial tear (n=2), conjunctival haemorrhage (n=1), Conjunctival hyperaemia (n=1), Retinal haemorrhage (n=1), Vitreous floaters (n=1), IOP increased (n=1) and eye irritation (n=1);
- In EU-Eylea: retinal pigment epithelial tear (n=2), Ocular hypertension (n=1), and IOP increased (n=1)

Similarly, up to week 52, comparable incidences of treatment related TEAEs and treatment related ocular TEAEs were reported between Mynzepli and EU-Eylea (4.9% vs 3.4% and 4.9% vs 2.9%, respectively). Up to week 52, additional events consisted of: conjunctival hyperaemia (n=2),

conjunctival haemorrhage (n=1), eye irritation (n=1), vision blurred (n=1) and endophtalmitis (n=1) in AVT-06 arm and Iridocylitis (n=1), Open angle glaucoma (n=1) in EU-Eylea arm.

The most reported PT was Ocular hyperaemia (n=3) and the PT occurring in ≥ 1% of the patients were Conjunctival haemorrhage (AVT-06 arm only) and Retinal pigment epithelial tear (in both arms). The observed ocular TEAEs are in line with the Eylea SmPC and/or EPAR.

Treatment-related non-ocular TEAEs (alanine amino transferase increased and gamma glutamyl transferase increased, possibly related) were reported by 1 (0.2%) participant in EU-Eylea. The case concerned a 57-years-old patient with medical history of hematuria and hyperlipidemia (treated by rosuvastatin 20 mg twice daily since march 2022). At screening the patient had GGT 101 U/L (normal range: 8-61 U/L), ALT 53 U/L (normal range: 0-41 U/L) and urinalysis revealed high levels of urobilinogen. On the same day, he presented a first episode of GGT and uribilinogen urine increase. The patient started treatment with Eylea in the left eye (study eye) on 21 Sep 2022. He presented, 168 days after the first and on the same day as another IVT administration of Eylea, another increase of GGT associated with ALAT increase (ALT 117 U/L, GGT 145 U/L) which both resolved without any taken action. The patient presented another increase in ALAT and GGT on day 280 after the first and on the same day as another IVT administration of Eylea. Both events resolved on week 52. The Investigator assessed the events of gamma glutamyl transferase increased (second episode) and alanine aminotransferase increased (first and second episode) as possibly related to Eylea. Considering the provided information above (in particular the reported medical history of the patient and TTO of the events), the causal relationship with Eylea is questionable.

Table 37: Incidence of Treatment-Related TEAEs up to Week 52 by SOC and PT (Safety Analysis Set)

	AVT06 (N=205)		**Eylea (N=205)**		**Total (N=410)**	
System Organ Class Preferred Term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Subjects with at least one Treatment-Related TEAE	10 (4.9)	14	7 (3.4)	11	17 (4.1)	25
Ocular TEAEs						
Subjects with at least one ocular TEAE	10 (4.9)	14	6 (2.9)	8	16 (3.9)	22
Eye disorders	8 (3.9)	12	5 (2.4)	6	13 (3.2)	18
Retinal pigment epithelial tear	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Conjunctival haemorrhage	2 (1.0)	2	0	0	2 (0.5)	2
Conjunctival hyperaemia	1 (0.5)	3	0	0	1 (0.2)	3
Eye irritation	1 (0.5)	2	0	0	1 (0.2)	2
Iridocyclitis	0	0	1 (0.5)	2	1 (0.2)	2
Ocular hypertension	0	0	1 (0.5)	1	1 (0.2)	1
Open angle glaucoma	0	0	1 (0.5)	1	1 (0.2)	1
Retinal haemorrhage	1 (0.5)	1	0	0	1 (0.2)	1
Vision blurred	1 (0.5)	1	0	0	1 (0.2)	1
Vitreous floaters	1 (0.5)	1	0	0	1 (0.2)	1
Investigations	1 (0.5)	1	1 (0.5)	2	2 (0.5)	3
Intraocular pressure increased	1 (0.5)	1	1 (0.5)	2	2 (0.5)	3
Infections and infestations	1 (0.5)	1	0	0	1 (0.2)	1
Endophthalmitis	1 (0.5)	1	0	0	1 (0.2)	1
Non-ocular TEAEs						
Subjects with at least one non-ocular TEAE	0	0	1 (0.5)	3	1 (0.2)	3
Investigations	0	0	1 (0.5)	3	1 (0.2)	3
Alanine aminotransferase increased	0	0	1 (0.5)	2	1 (0.2)	2
Gamma-glutamyltransferase increased	0	0	1 (0.5)	1	1 (0.2)	1

AE: Adverse Event, AESI: Adverse Event of Special Interest, m: Number of events, n: Number of subjects experiencing the event, TEAE: Treatment-Emergent AEs.
Adverse Events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 27.0.
Percentages are based on the total number of subjects in the Safety Analysis Set per treatment group.
Subjects with more than one event within a SOC or PT are counted only once for that SOC or PT.

2.4.8.3.1. Overview of TEAE by Subgroup

The included population consisted of more than 50% of the subjects being White (76.1% compared to 16.3% Asian, 6.6% Japan, and less than 1% for Black or African American, Multiple and Not reported) and from Europe (57.1% compared to 17.8% Americas, 6.8% Japan and 18.3% other). Twenty-eight (6.8%) subjects were Japanese. The mean (SD) BCVA score and CST at baseline was 55 (12.07) letters and 433.6 (122.79) µm; 52.2% of the subjects had baseline BCVA score ≥54 letters, and 50% of the subjects had baseline CST≥400 µm. For iris colour (IWRS), 46.8% had light irides (53.2% had non-light irides). Majority (91.5%) of the subjects were ADA negative at baseline and nAb status was unavailable in 94.1% of the population, negative in 5.4% and positive in 0.5% up to week 24.

No clinical meaningful differences were seen between Mynzepli and EU-Eylea regarding Geographical Origins, Race (Japanese, Non-Japanese), baseline BVCA, Iris colour and Baseline Central Subfield Thickness up to week 52.

2.4.8.4. Serious adverse events, deaths, and other significant events

Table 38: Incidence of Serious Adverse Events up to Week 52 by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
	n (%)	m	n (%)	m	n (%)	m
Subjects with at least one SAE	8 (3.9)	11	17 (8.3)	24	25 (6.1)	35
Ocular AEs						
Subjects with at least one ocular AE	1 (0.5)	1	0	0	1 (0.2)	1
Eye disorders	1 (0.5)	1	0	0	1 (0.2)	1
Lacrimation increased	1 (0.5)	1	0	0	1 (0.2)	1
Non-ocular AEs						
Subjects with at least one non-ocular AE	7 (3.4)	10	17 (8.3)	24	24 (5.9)	34
Infections and infestations	3 (1.5)	3	2 (1.0)	2	5 (1.2)	5
Pneumonia	2 (1.0)	2	0	0	2 (0.5)	2
Meningitis	1 (0.5)	1	0	0	1 (0.2)	1
Postoperative wound infection	0	0	1 (0.5)	1	1 (0.2)	1
Viral sepsis	0	0	1 (0.5)	1	1 (0.2)	1
Injury, poisoning and procedural complications	2 (1.0)	2	3 (1.5)	3	5 (1.2)	5
Lower limb fracture	0	0	1 (0.5)	1	1 (0.2)	1
Rib fracture	0	0	1 (0.5)	1	1 (0.2)	1
Road traffic accident	1 (0.5)	1	0	0	1 (0.2)	1
Thoracic vertebral fracture	0	0	1 (0.5)	1	1 (0.2)	1
Tibia fracture	1 (0.5)	1	0	0	1 (0.2)	1
Gastrointestinal disorders	1 (0.5)	1	3 (1.5)	3	4 (1.0)	4

System Organ Class Preferred Term	AVT06 (N=205) n (%)	m	Eylea (N=205) n (%)	m	Total (N=410) n (%)	m
Abdominal incarcerated hernia	0	0	1 (0.5)	1	1 (0.2)	1
Intestinal obstruction	0	0	1 (0.5)	1	1 (0.2)	1
Papilla of Vater stenosis	1 (0.5)	1	0	0	1 (0.2)	1
Rectal prolapse	0	0	1 (0.5)	1	1 (0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	4 (2.0)	4	4 (1.0)	4
Colon cancer	0	0	1 (0.5)	1	1 (0.2)	1
Endometrial adenocarcinoma	0	0	1 (0.5)	1	1 (0.2)	1
Malignant melanoma	0	0	1 (0.5)	1	1 (0.2)	1
Squamous cell carcinoma	0	0	1 (0.5)	1	1 (0.2)	1
Nervous system disorders	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Haemorrhage intracranial	1 (0.5)	1	0	0	1 (0.2)	1
Ischaemic stroke	0	0	1 (0.5)	1	1 (0.2)	1
Lumbar radiculopathy	0	0	1 (0.5)	1	1 (0.2)	1
Syncope	1 (0.5)	1	0	0	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders	0	0	3 (1.5)	3	3 (0.7)	3
Acute pulmonary oedema	0	0	1 (0.5)	1	1 (0.2)	1
Acute respiratory failure	0	0	1 (0.5)	1	1 (0.2)	1
Chronic obstructive pulmonary disease	0	0	1 (0.5)	1	1 (0.2)	1
Reproductive system and breast disorders	0	0	2 (1.0)	2	2 (0.5)	2
Ovarian cyst	0	0	1 (0.5)	1	1 (0.2)	1
Postmenopausal haemorrhage	0	0	1 (0.5)	1	1 (0.2)	1
Cardiac disorders	0	0	1 (0.5)	1	1 (0.2)	1
Cardiac failure	0	0	1 (0.5)	1	1 (0.2)	1
Ear and labyrinth disorders	0	0	1 (0.5)	2	1 (0.2)	2
Vertigo	0	0	1 (0.5)	2	1 (0.2)	2
Hepatobiliary disorders	1 (0.5)	1	0	0	1 (0.2)	1
Bile duct stone	1 (0.5)	1	0	0	1 (0.2)	1
Metabolism and nutrition disorders	1 (0.5)	1	0	0	1 (0.2)	1
Diabetic ketoacidosis	1 (0.5)	1	0	0	1 (0.2)	1
Musculoskeletal and connective tissue disorders	0	0	1 (0.5)	1	1 (0.2)	1
Osteoarthritis	0	0	1 (0.5)	1	1 (0.2)	1
Vascular disorders	0	0	1 (0.5)	1	1 (0.2)	1
Hypertensive crisis	0	0	1 (0.5)	1	1 (0.2)	1

Up to week 24, a higher proportion of serious TEAEs were reported in EU-Eylea with 3 (1.5%) participants in the Mynzepli group compared to 9 (4.4%) participants in the EU-Eylea group and no ocular SAEs were reported. Up to week 52, serious AEs were reported in 8 (3.9%) participants in the Mynzepli group and 17 (8.3%) participants in the Eylea group. All the SAEs except 1 in the fellow eye

(lacrimation increased) in the Mynzepli group were non-ocular AEs. All SAE were non-ocular and were not assessed as related to study treatment.

Reported SAEs up to week 24 were:
- Mynzepli arm: Syncope (n=1), Papilla of Vater stenosis (n=1), Bile duct stone (n=1), Pneumonia (n=1);
- EU-Eylea arm: Ischaemic stroke (n=1), Lumbar radiculopathy (n=1), Intestinal obstruction (n=1), Acute pulmonary oedema (n=1), Chronic Obstructive pulmonary disease (n=1), Cardiac failure (n=1), Vertigo(n=1), Rib fracture (n=1), Osteoarthritis (n=1) and Malignant melanoma (n=1).

UP to week 52, additional SAE consisted of: lacrimation increased (n=1), meningitis (n=1), road traffic incident (n=1), tibia fracture (n=1), haemorrhage intracranial (n=1), hepatobiliary disorders (n=1) and diabetic ketoacidosis (n=1) in AVT-06 arm and post-operative wound infection (n=1), viral sepsis (n=1), lower limb fracture (n=1), thoracic vertebral fracture (n=1), abdominal incarcerated hernia (n=1), ischaemic stroke (n=1), rectal prolapse (n=1), colon cancer (n=1), endometrial carcinoma (n=1), squamous cell carcinoma (n=1), acute respiratory failure (n=1), ovarian cyst (n=1), postmenopausal haemorrhage (n=1) and hypertensive crisis (n=1) in EU-Eylea arm..

Table 39: Incidence of TEAEs with Outcome of Death up to Week 52 by SOC and PT (Safety Analysis Set)

	AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
System Organ Class Preferred Term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Subjects with at least one TEAE leading to death	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
Non-ocular TEAEs						
Subjects with at least one non-ocular TEAE	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
Injury, poisoning and procedural complications	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Rib fracture	0	0	1 (0.5)	1	1 (0.2)	1
Road traffic accident	1 (0.5)	1	0	0	1 (0.2)	1
Infections and infestations	1 (0.5)	1	0	0	1 (0.2)	1
Meningitis	1 (0.5)	1	0	0	1 (0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.5)	1	1 (0.2)	1
Colon cancer	0	0	1 (0.5)	1	1 (0.2)	1
Nervous system disorders	1 (0.5)	1	0	0	1 (0.2)	1
Haemorrhage intracranial	1 (0.5)	1	0	0	1 (0.2)	1

Up to Week 52, 5 TEAEs led to the death of 3 participants (1 in Mynzepli and 2 in the Eylea group). An 89-year-old female had fallen which resulted in fractures of the rib and thoracic vertebrae with effect on the respiratory function. The primary cause of death was considered as rib fracture (due to fall from his own height) which led to thoracic coagulation and was assessed as not related to study treatment. The other death reported in EU-Eylea arm was due to colon cancer. One death was reported as road traffic accident (unrelated) in AVT06. The case concerned a 74-years-old patient who died following road traffic accident, haemorrhage intracranial ((intracranial bleed and subdural hematoma), and meningitis.

Table 40:Incidence of TEAEs with Outcome of Death up to Week 52 by SOC and PT (Safety Analysis Set)

	AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
System Organ Class Preferred Term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Subjects with at least one TEAE leading to death	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
Non-ocular TEAEs						
Subjects with at least one non-ocular TEAE	1 (0.5)	3	2 (1.0)	2	3 (0.7)	5
Injury, poisoning and procedural complications	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Rib fracture	0	0	1 (0.5)	1	1 (0.2)	1
Road traffic accident	1 (0.5)	1	0	0	1 (0.2)	1
Infections and infestations	1 (0.5)	1	0	0	1 (0.2)	1
Meningitis	1 (0.5)	1	0	0	1 (0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.5)	1	1 (0.2)	1
Colon cancer	0	0	1 (0.5)	1	1 (0.2)	1
Nervous system disorders	1 (0.5)	1	0	0	1 (0.2)	1
Haemorrhage intracranial	1 (0.5)	1	0	0	1 (0.2)	1

Up to week 24, incidences of AESI were well-balances between treatment group (4.4%, 9/205 participants in Mynzepli and 4.9%, 10/205 participants in EU-Eylea). The most common ocular AESI

reported in the study eye by Week 24 were Retinal pigment epithelial tear (2.4% Mynzepli vs 1.5% EU-Eylea), Retinal haemorrhage (1.0% EU-Eylea vs 0.5% AVT06), Hypertension (0.5% Mynzepli vs 1.0 EU-Eylea) and Blood pressure increased (1.0% Mynzepli vs 0% EU-Eylea). All other events were reported once in Mynzepli arm and/or EU-Eylea arm.

Similarly, up to week 52, the incidence of patients presenting at least one AESIs in the two treatment groups was comparable (6.8% in AVT-06 and 7.3%). The most common ocular AESIs reported in the study eye by Week 52 was retinal pigment epithelial tear reported in 5 participants (2.4%) in the Mynzepli group and in 4 participants (2.0.%) in the Eylea group.

Table 41: Incidence of AESIs up to Week 52 (Safety Analysis Set)

	AVT06 (N=205)		**Eylea (N=205)**		**Total (N=410)**	
AESI Preferred Term	**n (%)**	**M**	**n (%)**	**m**	**n (%)**	**m**
Subjects with at least one AESI	14 (6.8)	18	15 (7.3)	19	29 (7.1)	37
Ocular AESIs						
Eye disorders	6 (2.9)	7	8 (3.9)	10	14 (3.4)	17
Retinal pigment epithelial tear	5 (2.4)	5	4 (2.0)	4	9 (2.2)	9
Retinal haemorrhage	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Iridocyclitis	0	0	2 (1.0)	3	2 (0.5)	3
Vitritis	0	0	1 (0.5)	1	1 (0.2)	1
Investigations	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Intraocular pressure increased	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Infections and infestations	1 (0.5)	1	0	0	1 (0.2)	1
Endophthalmitis	1 (0.5)	1	0	0	1 (0.2)	1
Non-ocular AESIs						
Vascular disorders	6 (2.9)	7	4 (2.0)	5	10 (2.4)	12
Hypertension	6 (2.9)	7	3 (1.5)	3	9 (2.2)	10
Hypertensive crisis	0	0	1 (0.5)	1	1 (0.2)	1
Superficial vein thrombosis	0	0	1 (0.5)	1	1 (0.2)	1
Investigations	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Blood pressure increased	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Cardiac disorders	1 (0.5)	1	0	0	1 (0.2)	1
Angina pectoris	1 (0.5)	1	0	0	1 (0.2)	1
Nervous system disorders	0	0	1 (0.5)	1	1 (0.2)	1
Ischaemic stroke	0	0	1 (0.5)	1	1 (0.2)	1
Reproductive system and breast disorders	0	0	1 (0.5)	1	1 (0.2)	1
Postmenopausal haemorrhage	0	0	1 (0.5)	1	1 (0.2)	1

Abbreviations: AESI: Adverse Event of Special Interest, m: Number of events, n: Number of subjects experiencing the event. Percentages are based on the total number of subjects in the Safety Analysis Set per treatment group

Up to week 24, incidence of AESI related to treatment were comparable between treatment arms (2.0%, 4 in Mynzepli and 1.0%, 2 in EU-Eylea). Up to week 52, a total of 9 AESIs were considered to be related to treatment. Incidence of treatment-related AESI was comparable in the Mynzepli group (5 [2.4%]) and the Eylea group (3 [1.5%]). Out of 5 participants in the Mynzepli group reporting treatment-related AESIs, 2 participants had retinal pigment epithelial tear (mild or moderate, not recovered/not resolved in both cases and dose not changed), and 1 participant each had retinal haemorrhage (severe, drug withdrawn, resolved with sequela), endophtalmitis, and intraocular pressure increased. Two participants in the Eylea group had retinal pigment epithelial tear (mild or moderate, recovering/ resolving in both cases, dose not changed) and 1 had iridocyclitis.

Treatment related AESI were mostly mild and moderate in intensity. Only 1 participant (250512) had severe AESI (subretinal haemorrhage). The Investigator assessed the event of retinal haemorrhage as probably related to Mynzepli and the treatment was permanently discontinued. The event of retinal haemorrhage was reported as resolved with sequelae (subretinal fibrosis). Even though, treatment with Mynzepli was discontinued, as the occurrence of AESI in the study eye meets a condition for discontinuation, the participant was treated with aflibercept after the event. No safety concern was identified.

2.4.8.5. Laboratory findings

No clinical meaningful changes in the mean values were observed from baseline to week 4, 8, 24 and 52 for hematology, blood chemistry, urinalysis and other tests assessments, except some individual cases which were considered as TEAEs: haematology – in AVT-06 arm, 1 subject with eosinophilia increased and monocyte count increased; 1 subject with chronic lymphocytic leukaemia;1 subject with platelet count decreased; and in EU-Eylea arm, 1 subject with urine leukocyte esterase positive test; blood chemistry – in AVT-06, 2 subjects with high levels of GGT,1 subject with hyperkalaemia; 2 subjects with hyperglycaemia (including one with type 2 diabetes mellitus); 1 subject with hypercreatininaemia and in EU-Eylea arm, 2 subjects with high level of GGT; 1 subject with high level of GGT, ALT, ALP and AST; 1 subject with blood alkaline phosphatase increased; 2 subjects with blood creatinine increased. All of them were non-serious TEAE, mild or moderate in severity, not related to the treatment and resolved or were resolving at the time of the analysis. In the Eylea group, one patient (150201) had elevation of both GGT (78 U/L vs 101 U/L at baseline; reference range 5-36 U/L) at week 8 (60 U/L at week 4) and ALT (117 U/L vs 53 U/L at baseline; reference range 0-41 U/L) at week 24 (53 U/L at week 8). Changes in both parameters were considered as TEAEs and assessed as related to Eylea. No other clinical laboratory changes were assessed as related to Mynzepli nor Eylea.

At week 24, a higher proportion of patient with high systolic blood pressure was observed in Mynzepli group (Mynzepli vs Eylea: 11.2% vs 7.8%) while the incidence of patients with high diastolic blood pressure was comparable between treatment groups (Mynzepli vs Eylea: 2.9% vs 2.4%) however this is not considered as significant difference. Incidence of low respiratory rates was lower in Mynzepli group (Mynzepli vs Eylea: 0.5% vs 2.0%) and high respiratory rates (Mynzepli vs Eylea: 9.3% vs 7.3%) as well as high body temperatures (Mynzepli vs Eylea: 9.8% vs 9.8%) were comparable between groups at week 24. Up to week 52, the incidence of participants with high systolic blood pressure at Week 52 was comparable in both the treatment groups (Mynzepli vs Eylea: 10.7% vs 8.8%) and the incidence of participants with high diastolic blood pressure at Week 52 was higher in Eylea group (Mynzepli vs Eylea: 1.5% vs 4.9%) however this is not considered as significant difference. The incidence of participants with low respiratory rates was comparable between the two groups (Mynzepli vs Eylea: 0.0% vs 0.5%) and high respiratory rates at Week 52 was comparable between the two groups (Mynzepli vs Eylea: 9.8% vs 7.8%). The incidence of participants with high body temperature at Week 52 was similar between the two groups (Mynzepli vs Eylea: 9.8% vs 8.8%).

All abnormal vital signs assessed as TEAEs were non serious, mild or moderate in intensity and recovered; in AVT-06 arm, 1 subject with body temperature increased and 1 subject with blood pressure increased; in EU-Eylea arm, 3 subjects with blood pressure increased. No TEAEs related to abnormal changes in vital signs were assessed as related to Mynzepli nor Eylea groups. Abnormal clinically significant (ACS) changes which were captured as TEAEs consisted of in AVT-06 arm, 1 subject with atrial fibrillation and in EU-Eylea arm, 1 subject with atrial fibrillation, 1 subject with right ventricular hypertrophy and 1 subject with bundle branch block left. All were non-serious, mild, unrelated to aflibercept and resolving/resolved.

No safety concerns are raised regarding clinical laboratory evaluations, vital signs, and electrocardiogram.

Table 42: Summary of Intraocular Pressure Results (Safety Analysis Set)

Eye	Visit, Timepoint	Statistic	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
Study Eye	Baseline	n (%)	205 (100.0)	205 (100.0)	410 (100.0)
		Mean (SD)	15.0 (2.54)	15.0 (2.78)	15.0 (2.66)
		Median	15.0	15.0	15.0
		Min, Max	9, 21	7, 22	7, 22
	Day 1, 30-60 minutes postdose	n (%)	201 (98.0)	201 (98.0)	402 (98.0)
		Mean (SD)	16.8 (2.89)	16.9 (3.09)	16.8 (2.99)
		Median	17.0	17.0	17.0
		Min, Max	7, 24	9, 26	7, 26
	Week 4, predose	n (%)	205 (100.0)	204 (99.5)	409 (99.8)
		Mean (SD)	14.4 (2.61)	14.4 (2.56)	14.4 (2.58)
		Median	14.0	14.0	14.0
		Min, Max	9, 20	8, 19	8, 20
	Week 4, 30-60 minutes postdose	n (%)	202 (98.5)	201 (98.0)	403 (98.3)
		Mean (SD)	16.5 (2.96)	17.1 (3.12)	16.8 (3.05)
		Median	17.0	17.0	17.0
		Min, Max	9, 28	8, 25	8, 28
	Week 8, predose	n (%)	204 (99.5)	202 (98.5)	406 (99.0)
		Mean (SD)	14.6 (2.48)	14.5 (2.75)	14.5 (2.61)
		Median	15.0	15.0	15.0
		Min, Max	8, 20	8, 27	8, 27
	Week 8, 30-60 minutes postdose	n (%)	203 (99.0)	197 (96.1)	400 (97.6)
		Mean (SD)	16.6 (2.91)	17.4 (4.37)	17.0 (3.72)
		Median	17.0	17.0	17.0
		Min, Max	10, 26	9, 60	9, 60
Study Eye	Week 16, predose	n (%)	201 (98.0)	194 (94.6)	395 (96.3)
		Mean (SD)	14.7 (2.47)	14.5 (2.69)	14.6 (2.58)
		Median	15.0	14.0	15.0
		Min, Max	8, 20	8, 20	8, 20
	Week 16, 30-60 minutes postdose	n (%)	198 (96.6)	191 (93.2)	389 (94.9)
		Mean (SD)	16.7 (2.60)	17.0 (3.01)	16.8 (2.81)
		Median	17.0	17.0	17.0
		Min, Max	9, 23	10, 30	9, 30
	Week 24, predose	n (%)	197 (96.1)	194 (94.6)	391 (95.4)
		Mean (SD)	14.6 (2.61)	14.7 (2.73)	14.6 (2.66)
		Median	15.0	15.0	15.0
		Min, Max	8, 20	8, 22	8, 22
	Week 24, 30-60 minutes postdose	n (%)	196 (95.6)	193 (94.1)	389 (94.9)
		Mean (SD)	16.6 (2.46)	16.9 (3.25)	16.8 (2.88)
		Median	17.0	17.0	17.0
		Min, Max	10, 23	10, 28	10, 28
	Week 32, predose	n (%)	197 (96.1)	195 (95.1)	392 (95.6)
		Mean (SD)	15.0 (2.68)	14.7 (2.73)	14.8 (2.71)
		Median	15.0	15.0	15.0
		Min, Max	8, 22	8, 21	8, 22

Eye	Visit, Timepoint	Statistic	AVT06 (N=205) n (%)	Eylea (N=205) n (%)	Total (N=410) n (%)
	Week 32, 30-60 minutes postdose	n (%)	194 (94.6)	191 (93.2)	385 (93.9)
		Mean (SD)	16.9 (2.72)	17.1 (3.11)	17.0 (2.92)
		Median	17.0	17.0	17.0
		Min, Max	10, 24	10, 27	10, 27
Study Eye	Week 40, predose	n (%)	195 (95.1)	186 (90.7)	381 (92.9)
		Mean (SD)	14.9 (2.43)	14.8 (2.70)	14.9 (2.56)
		Median	15.0	15.0	15.0
		Min, Max	8, 20	9, 26	8, 26
	Week 40, 30-60 minutes postdose	n (%)	195 (95.1)	185 (90.2)	380 (92.7)
		Mean (SD)	17.1 (2.43)	17.3 (3.04)	17.2 (2.74)
		Median	18.0	17.0	18.0
		Min, Max	10, 22	8, 29	8, 29
	Week 48, predose	n (%)	191 (93.2)	187 (91.2)	378 (92.2)
		Mean (SD)	14.7 (2.43)	14.9 (2.68)	14.8 (2.56)
		Median	15.0	15.0	15.0
		Min, Max	10, 19	8, 25	8, 25
	Week 48, 30-60 minutes postdose	n (%)	189 (92.2)	186 (90.7)	375 (91.5)
		Mean (SD)	16.9 (2.43)	17.2 (2.83)	17.0 (2.63)
		Median	17.0	17.0	17.0
		Min, Max	9, 22	9, 29	9, 29
	Week 52, predose	n (%)	191 (93.2)	189 (92.2)	380 (92.7)
		Mean (SD)	14.6 (2.54)	14.9 (2.52)	14.7 (2.53)
		Median	15.0	15.0	15.0
		Min, Max	8, 21	8, 25	8, 25
Fellow Eye	Baseline	n (%)	205 (100.0)	205 (100.0)	410 (100.0)
		Mean (SD)	15.1 (2.69)	14.9 (2.60)	15.0 (2.64)
		Median	15.0	15.0	15.0
		Min, Max	9, 22	10, 22	9, 22
Fellow Eye	Day 1, 30-60 minutes postdose	n (%)	80 (39.0)	88 (42.9)	168 (41.0)
		Mean (SD)	15.3 (3.15)	15.1 (2.83)	15.2 (2.98)
		Median	15.0	15.0	15.0
		Min, Max	7, 22	10, 21	7, 22

Max: maximum; Min: minimum; n: number of subjects; SD: standard deviation.
Intraocular pressure is recorded in mmHg.
One eye will be selected as the study eye based on inclusion and exclusion criteria. If subject meets eligibility criteria in both eyes, the eye with the worse visual acuity will be selected as the study eye.

From ophthalmic parameters, the intraocular pressure (IOP), biomicroscopy investigation and indirect ophthalmoscopy were performed. Up to week 52, mean (SD) intraocular pressure in the study eye at baseline for Mynzepli and EU-Eylea were comparable (14.6 (2.54) Mynzepli and 14.9 (2.52) EU-Eylea). Similarly, no significant differences were observed between treatment arms regarding intraocular pressure in the study eye at Day 1, Week 4, Week 8, Week 16, Week 24 and Week 52. Mean (SD)

intraocular pressure in the fellow eye at baseline and Day 1 30-60 minutes post dose was comparable between Mynzepli and EU-Eylea groups.

Biomicroscopy results were presented in the study report. Abnormal clinical changes for external examination, conjunctiva examination, cornea examination, anterior chamber examination, iris examination and lens examination were low (proportion ≤1%) and occurring in single participants, except for lens examination, in both treatment arms and comparable. Abnormal clinically significant findings in the study eye for lens examination were slightly more reported up to week 24 (5.4% Mynzepli vs 2.9% in EU-Eylea) however similar results were seen in the fellow eye (4.9% in Mynzepli vs 3.4% in EU-Eylea). Similar results were observed up to week 52.

Indirect ophthalmoscopy results were presented in the study report. Up to week 24, abnormal clinical significant findings for retinal, retinal vasculature and vitreous were comparable between treatment arms. Abnormal clinical significant findings in the study eye for optic nerve head (papilla) were slightly higher in EU-Eylea arm (2.4% EU-Eylea arm vs 0.5% Mynzepli arm) however similar results were observed for the fellow eye. Abnormal clinical significant findings in the study eye for macula were higher in Mynzepli arm compared to EU-Eylea (43.4% vs 34.1%) however, such difference was also observed at baseline (52.7% Mynzepli vs 43.4% in EU-Eylea). Similar results were observed up to week 52.

Overall, no safety concerns are raised regarding biomicroscopy and indirect ophthalmoscopy results up to week 52. Up to week 52, there were no notable differences in mean changes from baseline in physical examination findings and no abnormal clinically significant physical examination were assessed as related to Mynzepli nor EU-Eylea arms. All TEAEs were non-serious mild or moderate and resolved or resolving.

No safety concerns are raised regarding physical examination.

2.4.8.6. In vitro biomarker test for patient selection for safety

Not applicable.

2.4.8.7. Safety in special populations

Not applicable.

2.4.8.8. Immunological events

Regarding immunogenicity, in the scientific advice (EMA/SA/0000063900), it was concluded that in terms of immunogenicity assessment for the biosimilar products, the wet AMD patient population is agreed as a sensitive patient population for the biosimilar. Although, it is uncertain whether this is the most sensitive trial population compared to other indications, notably including younger age groups it is however acknowledged that the proportion of patients who developed ADAs was low across all indications. Moreover, the safety profile is also similar across the indications approved for Eylea.

Information on the risk of immunogenicity is described in sections 4.4 and 4.8 of SmPC in line with the reference medicinal product. TEAEs were assessed also by ADA status resp. nAb status in patients. In the ADA positive subgroup, the incidence of subjects with treatment-emergent AESIs was comparable between treatment groups (Mynzepli: 4.1%; Eylea: 6.3%). Similarly, in the nAb positive subgroup the incidence of subjects with treatment-emergent AESIs was comparable (Eylea: 6.1% vs Mynzepli: 5%). The incidence of TEAEs, AESI or serious TEAEs was similar between both treatment arms, therefore, no impact on overall Mynzepli safety profile compared to reference product Eylea is expected.

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

Not applicable.

2.4.8.10. Discontinuation due to adverse events

Two patients (1.0%) had TEAEs leading to discontinuation of study treatment in Mynzepli arm (retinal haemorrhage and rheumatoid arthritis) while 4 patients (1.5%) had TEAEs leading to discontinuation of study treatment in EU-Eylea arm (detachment of retinal pigment epithelium, vitritis, IOP increased and Rib fracture).

In the CSR is stated that a total of 16 subjects (3.9%) discontinued the treatment prior to Week 24. The main reasons were: lost to follow-up (6 subjects), withdrawal of consent (3 subjects), AEs (3 subjects), physician decision (2 subjects), death (1 subject) and other reason (1 subject). All subject who discontinued the treatment also discontinued the study, the remaining 394 (96.1%) subjects completed the study up to Week 24. From the total number of 16 discontinuations, the **AEs reason** were reported in **3 patients who discontinued the study treatment**. The patient no 160308 with detachment of retinal pigment epithelium and vitritis then discontinued the study due withdrawal consent, therefore the number of subjects who discontinued the study due AEs was only 2.

However, the following information can be obtained from the final safety evaluation (chapter 12.0, pg. 119) and safety summary: 5 subjects (1.2 %) reported TEAEs that led to the d**iscontinuation of the study treatment** – 2 (1%) from the Mynzepli arm with 2 events and 3 (1.5%) from the Eylea arm with 4 events. Of these subjects, 1 patient in the Mynzepli (1 TEAE - retinal haemorrhage) and 2 patients (3 TEAEs – detachment of retinal pigment epithelium and vitritis at the same time in one subject, IOP increased) in the Eylea group reported ocular AEs. The non-ocular TEAEs were rheumatoid arthritis in Mynzepli patient and rib fracture in Eylea patient. A total of 4 subjects (2 in each group) reported TEAE which led to **discontinuation from the study**. It was stated by the applicant that also the patient 110905 (rib fracture, death) and patient 250512 (retinal haemorrhage, the study was ended after Week 24, although the AE leading to discontinuation started prior Week 24 and the treatment administered at Week 24 was the last one) are counted here. This is acceptable.

All narratives for the above-mentioned patients can be found in the documentation. The reported AEs which led to discontinuation were assessed as not related or unlikely to be related to the study treatment, only the patient No 250512 reported (sub)retinal haemorrhage (AESI) which was judged as probably related to AVT06. Retinal haemorrhage is already listed in the SmPC of Eylea with frequency very common, therefore the occurrence of this AE is expected.

In conclusion, it is agreed that no clinically meaningful differences were seen across all treatment groups in terms of TEAEs leading to IP discontinuation.

Table 43:Incidence of TEAEs Leading to Discontinuation of Study Treatment up to Week 52 by SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	**AVT06 (N=205)**		**Eylea (N=205)**		**Total (N=410)**	
	n (%)	**m**	**n (%)**	**M**	**n (%)**	**m**
Subjects with at least one TEAE leading to discontinuation of study treatment	4 (2.0)	4	5 (2.4)	7	9 (2.2)	11
Ocular TEAEs						
Subjects with at least one ocular TEAE	1 (0.5)	1	2 (1.0)	3	3 (0.7)	4
Eye disorders	1 (0.5)	1	1 (0.5)	2	2 (0.5)	3

System Organ Class Preferred Term	AVT06 (N=205)		Eylea (N=205)		Total (N=410)	
	n (%)	m	n (%)	M	n (%)	m
Detachment of retinal pigment epithelium	1 (0.5)	1	1 (0.5)	2	2 (0.5)	3
Retinal haemorrhage	0	0	1 (0.5)	1	1 (0.2)	1
Vitritis	1 (0.5)	1	0	0	1 (0.2)	1
Investigations	0	0	1 (0.5)	1	1 (0.2)	1
Intraocular pressure increased	0	0	1 (0.5)	1	1 (0.2)	1
Non-ocular TEAEs						
Subjects with at least one non-ocular TEAE	3 (1.5)	3	3 (1.5)	4	6 (1.5)	7
Injury, poisoning and procedural complications	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Rib fracture	0	0	1 (0.5)	1	1 (0.2)	1
Road traffic accident	1 (0.5)	1	0	0	1 (0.2)	1
Musculoskeletal and connective tissue disorders	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Rheumatoid arthritis	1 (0.5)	1	0	0	1 (0.2)	1
Spinal pain	0	0	1 (0.5)	1	1 (0.2)	1
Infections and infestations	0	0	1 (0.5)	1	1 (0.2)	1
Postoperative wound infection	0	0	1 (0.5)	1	1 (0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.5)	1	1 (0.2)	1
Colon cancer	0	0	1 (0.5)	1	1 (0.2)	1
Nervous system disorders	1 (0.5)	1	0	0	1 (0.2)	1
Diplegia	1 (0.5)	1	0	0	1 (0.2)	1

Up to week 52, TEAEs leading to discontinuation of the study treatment were reported in 4 participants (2.0%; 4 AEs) in the Mynzepli group and 5 participants (2.4%; 7 AEs) in the Eylea group. Of these, 3 participants (1 in the Mynzepli and 2 in Eylea group) reported 4 ocular AEs.

2.4.8.11. Post marketing experience

Not applicable.

2.4.9. Discussion on clinical safety

Safety assessment

The safety of Mynzepli (as a proposed similar biological medicinal product to Eylea) is supported by AVT06-GL-C01, a single comparative 52-weeks phase III randomized, double-masked, parallel-group, multicenter clinical study (117 study centres, 14 countries. In the two scientific advices given for AVT06, it was agreed that a single efficacy and safety study, AVT06-GL-301, is adequate to demonstrate clinical similarity of Mynzepli and EU-Eylea. A separate comparative pharmacokinetic study was considered as not warranted nor useful to support similarity. Initially, the applicant provided separate analysis of data up to 24-weeks which was assessed in the day 80 clinical assessment report and on D-120 LoQ, the applicant provided complete results up to 52-weeks.

Regarding the schedule of assessment, it was recommended in the scientific advice that immunogenicity testing at baseline, Week 8, 12, 24 (or 2-3 samples the first 1-4 months) and 52 would be sufficient. In study AVT06-GL-C01, immunogenicity blood samplings were done at baseline, Week 4, 8, 16, 24, and 52 which is acceptable. Additionally, regarding the safety assessment the

applicant was advised to add a visit for all subjects at day 1 or 2, and one week after the first injection, and to evaluate safety (and preferably also efficacy) on a monthly basis, at least up to Week 24 (EMA/SA/0000063900, Sept 2021). In study AVT06-GL-C01, AE/SAE/AESI will be reviewed at every scheduled visit (baseline, week 4, 8, 16, 24, 32, 40, 48 and 52) and a safety phone call was performed 3 days (±1 day) after the study treatment administration. The applicant did not follow the advice regarding the addition of a visit at week 12 and 20 to follow a monthly evaluation up to at least week 24, although this would have been preferable, this is considered as acceptable.

Mynzepli is a biosimilar of aflibercept which will be available in two presentations: a 2 mg/0.05 mL single-dose glass vial and a 2 mg/0.05 mL single-dose pre-filled glass syringe. While using two similar container systems (vial vs vial or PFS vs PFS) would have been the preferred approach, it is recognised that the Mynzepli PFS is still currently under development and that its safety profile should not majorly differ from the known profile of the Mynzepli vial, moreover blinding was performed as to ensure that the safety assessments were unbiased Mynzepli is composed of Polysorbate, sucrose, α,α-trehalose and histidine which use are established in other formulations for intravitreal use. Another component is Poloxamer 188 which is not regarded as a novel nor an excipient generally associated with any theoretical safety concerns; however, its use in intravitreal formulations has not been established.

Patient exposure

A total of 413 participants were included in the study (randomized as follows: Mynzepli – 206, Eylea – 207). The safety analysis set (patients) included 410 participants (205 participants each in Mynzepli and Eylea treatment arms) who receive at least 1 dose of study treatment and consisted of male and female participant's ê50 years of age with neovascular (wet) AMD with a 1:1 ratio of patients treated with 2 mg (0.05 mL) IVT Mynzepli and 2 mg (0.05 mL) IVT EU-Eylea treatment arms which is acceptable for the determination of the basic safety profile.

An 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 (ê1/100 to <1/10) and very common (ê1/10) adverse events. However, it is too small to inform on less frequently occurring adverse events, this approach is considered adequate for biosimilar development.

The number of doses and the duration of exposure were comparable Up to 52 weeks, patients in study received a median total number of 8 injections for 88.3% in Mynzepli arm and 85.9% in EU-Eylea arm. The overall duration of exposure is of 46.523 weeks in Mynzepli and 45.22 weeks in EU-Eylea arms. The mean total dose received is of 15.5 mg in Mynzepli arm and 15.2 mg in EU-Eylea. The Compliance to study treatment was well observed with a mean around 99% in both treatment arms (99.45% in Mynzepli and 98.68% in Eylea There are no safety concerns regarding to patient exposure at the moment. Demographic and baseline characteristics were comparable between both treatment arms although discussion were further required (see *Clinical Efficacy* section for comments).

TEAEs (type, frequency, relatedness)

Overview of TEAEs up to Week 24 and 52 have been presented. Up to week 52, 63.4% of the patients experienced 762 TEAEs. Overall, a total of 47.8% and 68.8% of the patients in Mynzepli and 46.3% and 58.0% of the patients in EU-Eylea experienced at least one adverse events up to week 24 and 52 respectively. TEAEs were reported in comparable incidences between Mynzepli arm (46.3%, 95 participants up to week 24 and 67.8%, 139 participants up to week 52) compared to EU-Eylea arm (43.4%, 89 participants up to week 24 and 56.1%, 115 participants up to week 52). The risk adjusted incidence rate of TEAEs (number of subjects with events per 100 total person-years at risk calculated by (Number of subjects with TEAE/Total PY) *100) up to Week 24 in the Mynzepli group was higher

(139.5%) compared to the Eylea group (128.5%). Similarly, up to week 52, the riskadjusted incidence rate of TEAEs in the Mynzepli group was 129.8% and in the Eylea group was 102.1%.

The most reported SOC were Eye disorders (20.0% in Mynzepli arm and 18.5% in EU-Eylea arm up to week 24 and 31.7% vs 26.8% up to week 52) and Infections and infestations (higher in Mynzepli with 14.6% vs 10.7% in EU-Eylea arm and 22.4% vs 20.5% up to week 52). The most reported PT (>5% of the participants) was nAMD in the fellow eye (5.9 in Mynzepli arm and 6.8% in EU-Eylea arm up to week 24 and 10.7% vs 10.2% up to week 52) and nasopharyngitis (higher in Mynzepli with 6.8% vs 2.0% in EU-Eylea arm up to week 24 and 9.3% vs 3.4% up to week 52).

Ocular TEAEs in the study eye were reported in comparable proportions between Mynzepli and EU-Eylea arms up to week 52 (16.1%, 33 participants and 15.6%, 32 participants up to week 24 and 24.9%, 51 participants in Mynzepli and 21.5%, 44 participants in EU-Eylea). Ocular AEs in the fellow eye occurred in slightly higher proportion up to week 24 in the Mynzepli arm (11.7% vs 7.8% in EU-Eylea arm) and week 52 (20.0% vs 14.6% in EU-Eylea arm). TEAEs were majorly mild to moderate in severity, severe TEAE was reported in 2 (1.0%) participants in the Mynzepli group. No serious ocular TEAEs occurred in both AVT-06 and Eylea group. Non-ocular AEs were reported in comparable proportions between treatment arms (33.7% in Mynzepli arm and 32.2% in EU-Eylea arm up to week 24 and 52.7% in Mynzepli and 45.4% in EU-Eylea up to week 52) Severe non-ocular TEAEs were more reported in Eylea arm (5.9% vs 1.5%). Serious non-ocular TEAEs were also more reported in Eylea arm (8.3% vs 2.9%). None were assessed as related to study treatment. Non-Ocular TEAEs leading to study discontinuation were reported in comparable proportions (1.5% in AVT-06 and 1.0% in Eylea).

Ocular TEAEs (study eye and fellow eye) occurring in more than 1% of the participants were reported in comparable proportions between treatment arms up to week 24 and week 52. Most reported PT consisted of conjunctival haemorrhage (2.9% Mynzepli arm vs 2.0% EU-Eylea arm up to week 24 and 3.9% Mynzepli arm vs 2.4% EU-Eylea arm up to week 52), retinal pigment epithelial tear (2.4% Mynzepli arm vs 1.5% EU-Eylea arm up to week 24 and 2.4% Mynzepli arm vs 2.0 % EU-Eylea arm up to week 52), vitreous floaters (2.4% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 2.9% Mynzepli arm vs 1.5% EU-Eylea arm up to week 52), visual acuity reduced (1.0% Mynzepli arm vs 1.5% EU-Eylea arm up to week 24 and week 52), eye pain (1.0% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 1.0% Mynzepli arm vs 1.5% EU-Eylea arm up to week 52), cataract (0.5% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 2.0% Mynzepli arm vs 2.4 % EU-Eylea arm up to week 52), punctuate keratitis (1.0% Mynzepli arm vs 0.5% EU-Eylea arm up to week 24 and 52), retinal haemorrhage (0.5% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 1.0% Mynzepli arm vs 1.0% EU-Eylea up to week 52), conjunctival hyperaemia (1.0 % Mynzepli arm vs 0% EU-Eylea arm up to week 24 and 52), macula scar (1.0% Mynzepli arm vs 0% EU-Eylea arm up to week 24 and 52), conjunctivis viral (1.0% Mynzepli arm vs 0% EU-Eylea arm up to week 24 and 52) and IOP increased (0.5% Mynzepli arm vs 1.0% EU-Eylea arm up to week 24 and 52). These events, except macular scar and conjunctivitis viral are all events reported with aflibercept. The risk adjusted rate for most reported ocular TEAEs up to week 24 were neovascular age related macular degeneration (Mynzepli: 12.9%; Eylea: 15.5%), conjunctival haemorrhage (Mynzepli: 6.4%; Eylea: 4.3%), retinal pigment epithelial tear and vitreous floaters (Mynzepli: 5.3%; Eylea: 3.2%). For the fellow eye, the most reported ocular TEAEs was nAMD which was reported in comparable proportions between treatment arms (10.2% AVT-06 vs 9.8% in Eylea). TEAEs in the SOC eye disorders occurring in >=1% of Subjects were reported in comparable proportions between treatment arms.

Non-ocular TEAEs occurring in more than 1% of the participants were consistent with the study population and consisted for the most reported of headache, osteoarthritis, back pain, urinary tract infection, COVID-19 and rhinitis. All events reported in more than 1% of the population were observed in comparable proportions between treatment arms except nasopharyngitis which was more reported for Mynzepli (6.8% vs 2.0% in EU-Eylea arm up to week 24 and 9.3% vs 3.4% up to week 52).

Nasopharyngitis was not assessed as related to the study treatment in any of the subjects. The risk adjusted ratio for most reported non-ocular TEAEs were nasopharyngitis (Mynzepli: 15.3%; Eylea: 4.3%), headache (Mynzepli: 8.6%; Eylea: 6.5%) and osteoarthritis (Mynzepli: 0.0%; Eylea: 5.4%). It is acknowledged that nasopharyngitis is a common ailment in elder population, all cases were mild to moderate in severity, resolved and none were assessed as related to study drug.

The severity of each AE was recorded as mild, moderate, or severe. Overall TEAEs were mainly mild to moderate in severity with comparable proportions between treatment arms (33.7% AVT-06) vs 28.8% (EU-Eylea) and 10.7% AVT-06) vs 11.2% (EU-Eylea) up to week 24 and 46.3% (AVT-06) vs 33.0% (EU-Eylea) and 19.0% (AVT-06) vs 17.1% (EU-Eylea) up to week 52). A slightly higher proportion of TEAEs with mild severity were reported in Mynzepli arm (33.7% vs 28.8% in EU-Eylea arm up to week 24 and 46.3% vs 32.2% up to week 52). For treatment related TEAEs, 6 subjects had 10 mild TEAEs (Mynzepli: 4 subjects and 7 TEAEs; Eylea: 2 subjects and 3 TEAEs) and 5 subjects had 5 moderate TEAEs (Mynzepli: 2 subjects and 2 TEAEs; Eylea: 3 subjects and 3 TEAEs). Up to week 52, out of 17 subjects experiencing treatment-related TEAEs, 10 subjects had 17 mild TEAEs (Mynzepli: 6 subjects and 10 TEAEs; Eylea: 4 subjects and 7 TEAEs), 6 subjects had 7 moderate TEAEs (Mynzepli: 3 subjects and 3 TEAEs; Eylea: 3 subjects and 4 TEAEs), and 1 subject in the Mynzepli group had a severe TEAE (retinal haemorrhage). Ocular TEAEs in the study eye were mainly mild to moderate (12.2% and 2.9% up to week 24 and 19.5 % and 4.4% up to week 52 in Mynzepli arm and 10.7% and 4.9% up to week 24 and 15.1% and 6.3% up to week 52 in EU-Eylea arm). Severe TEAE were seen in low proportions in both treatment arm (2.0% in Mynzepli arm and 2.9% in EU-Eylea arm up to week 24 and 2.0% in Mynzepli and 4.9% in EU-Eylea up to week 52). One severe ocular TEAEs in the study eye and assessed as related to study drug was reported in Mynzepli arm. Regarding ocular TEAEs, for the SOC Eye disorders, events were mild to moderate with comparable proportions and two severe events (visual acuity reduced and retinal haemorrhage) were reported in Mynzepli arm compared to none in EU-Eylea arm.

Regarding non-ocular TEAEs up to week 24, severe events were low and consisted of 2 events in AVT-06 (2 patients in total: pneumonia and back pain) and 8 events in EU-Eylea arm (6 patients in total: lumbar radiculopathy, schaemic stroke, osteoarthritis, intestinal obstruction, acute pulmonary oedema, cardiac failure and superficial vein thrombosis). Up to week 52, 8 additional non-ocular TEAEs were reported in 4 patients in EU-Eylea arm: lower limb fracture, syncope, acute respiratory failure, pulmonary oedema, superficial vein thrombosis, viral sepsis, endometrial cancer, and ovarian cyst.

TEAE assessed as related to study medication by the investigator were few and proportions were comparable between treatment arms up to week 24 (3.4%, 7 subjects experienced 10 TEAEs in Mynzepli and 2.4%, 5 subjects experienced 6 TEAEs in EU-Eylea) and up to week 52 (4.9%, 10 subjects experienced 14 TEAEs in Mynzepli and 3.4%, 7 subjects experienced 11 TEAEs in EU-Eylea). Most of the subjects experienced treatment-related ocular TEAEs. Ocular TEAEs in the study eye assessed as treatment related were slightly higher in Mynzepli arm (3.4% vs 2.0% in EU-Eylea arm up to week 24 and 4.9% vs 2.9% in EU-Eylea arm up to week 52). The observed ocular TEAEs are in line with the Eylea SmPC and/or EPAR.

Up to week 24, comparable incidences of treatment related TEAEs and treatment related ocular TEAEs were reported between Mynzepli and EU-Eylea (3.4% vs 2.4% and 3.4% vs 2.0%, respectively). Up to week 24, these events consisted of in Mynzepli: retinal pigment epithelial tear (n=2), conjunctival haemorrhage (n=1), conjunctival hyperaemia (n=1), retinal haemorrhage (n=1), vitreous floaters (n=1), IOP increased (n=1) and eye irritation (n=1); and in EU-Eylea : retinal pigment epithelial tear (n=2), ocular hypertension (n=1), and IOP increased (n=1). Similarly, up to week 52, comparable incidences of treatment related TEAEs and treatment related ocular TEAEs were reported between Mynzepli and EU-Eylea (4.9% vs 3.4% and 4.9% vs 2.9%, respectively). Up to week 52, additional

events consisted of: conjunctival hyperaemia (n=2), conjunctival haemorrhage (n=1), eye irritation (n=1), vision blurred (n=1) and endophtalmitis (n=1) in AVT-06 arm and iridocyclitis (n=1), open angle glaucoma (n=1) in EU-Eylea arm.

The most reported PT was Ocular hyperaemia (n=3) and the PT occurring in ≥ 1% of the patients were conjunctival haemorrhage (AVT-06 arm only) and Retinal pigment epithelial tear (in both arms).

One subject in the Eylea group (ID 150201) had 2 non-ocular TEAEs (Alanine aminotransferase increased and Gamma-glutamyltransferase increased) considered possibly related to Eylea. Both TEAEs were mild (ALT 117 U/L, GGT 78 U/L), the dose was not changed, and they were resolving/resolved. Considering the information provided in the narrative, in particular the reported medical history of the patient and TTO of the events, the causal relationship with Eylea is questionable.

AESIs, SAEs, serious ADRs, deaths

Serious TEAEs were more reported in the EU-Eylea arm (4.4% vs 1.0% in Mynzepli up to week 24 and 8.3% vs 3.4% in AVT-06) and none were assessed as related to study treatment. Up to week 24, a higher proportion of serious TEAEs were reported in EU-Eylea with 3 (1.5%) participants in the Mynzepli group compared to 9 (4.4%) participants in the EU-Eylea group and no ocular SAEs were reported. Up to week 52, serious AEs were reported in 8 (3.9%) participants in the Mynzepli group and 17 (8.3%) participants in the Eylea group. All the SAEs except 1 in the fellow eye (lacrimation increased) in the Mynzepli group were non-ocular AEs. All SAE were not assessed as related to study treatment.

Up to Week 52, 5 TEAEs led to the death of 3 participants (1 in Mynzepli and 2 in the Eylea group). An 89-year-old female in the Eylea group had fallen which resulted in fractures of the rib and thoracic vertebrae with effect on the respiratory function. The primary cause of death was considered as rib fracture (due to fall from his own height) which led to thoracic coagulation and was assessed as not related to study treatment. The other death reported in EU-Eylea arm was due to colon cancer considered not related to study treatment. One death was reported as road traffic accident (unrelated) in AVT06. The case concerned a 74-years-old patient who died following road traffic accident, haemorrhage intracranial ((intracranial bleed and subdural hematoma), and meningitis.

Incidences of treatment emergent AESI were well-balanced (4.4% and 6.8%in Mynzepli and 4.9% and 7.3% in EU-Eylea) up to week 24 and week 52 respectively. Treatment emergent AESI in the study eye occurred in similar proportion (3.9% in Mynzepli and 4,4% EU-Eylea arm). The most common ocular AESI reported were retinal pigment epithelial tear (2.4% Mynzepli vs 1.5% EU-Eylea), retinal haemorrhage (1.0% in both EU-Eylea and AVT06), hypertension (2.9% Mynzepli vs 1.0 EU-Eylea) and blood pressure increased (0.5% Mynzepli vs 0.5% EU-Eylea) and iridocyclitis (0% Mynzepli vs 1.0% EU-Eylea). All other events were reported once in Mynzepli arm and/or EU-Eylea arm. The most common ocular AESIs reported in the study eye by Week 52 was retinal pigment epithelial tear reported in 5 participants (2.4%) in the Mynzepli group and in 4 participants (2.0%) in the Eylea group.

Incidences of AESI related to treatment were comparable between treatment arms (2.0%, 4 in Mynzepli and 1.0%, 2 in EU-Eylea up to week 24 (2.4% in AVT-06 and 1.5% in EU-Eylea up to week 52).Up to week 52, a total of 9 AESIs were considered to be related to treatment. Incidence of treatment-related AESI was comparable in the Mynzepli group (5 [2.4%]) and the Eylea group (3 [1.5%]). Out of 5 participants in the Mynzepli group reporting treatment-related AESIs, 2 participants had retinal pigment epithelial tear (mild or moderate, resolving in both cases and dose not changed), and 1 participant each had retinal haemorrhage (severe, drug withdrawn, resolved with sequelae), endophtalmitis (moderate, resolved), and intraocular pressure increased (moderated, resolved, dose not changed). Two participants in the Eylea group had retinal pigment epithelial tear (mild or

moderate, recovering/ resolving in both cases, dose not changed) and 1 had iridocyclitis (mild, resolved, treatment interrupted).

Treatment related AESI were mostly mild and moderate in intensity. Only 1 participant (250512) had severe AESI (subretinal haemorrhage). The Investigator assessed the event of retinal haemorrhage as probably related to Mynzepli and the treatment was permanently discontinued. The event of retinal haemorrhage was reported as resolved with sequelae (subretinal fibrosis). Even though, treatment with Mynzepli was discontinued, as the occurrence of AESI in the study eye meets a condition for discontinuation, the participant was treated with aflibercept after the event. No safety concern was identified.

Discontinuation due to adverse events

TEAE leading to study treatment discontinuation or study discontinuation were low and comparable between treatment arms up to week 24 (respectively 1.0% in Mynzepli and 1.5% and 1.0% in EU-Eylea) and week 52 (respectively 2.0% and 1.5% in Mynzepli and 2.4 % and 2.0% in EU-Eylea). One TEAE leading to study treatment and study discontinuation was assessed as related to study treatment in Mynzepli arm up to week 52 (retinal haemorrhage).

In the CSR is stated that a total of 16 subjects (3.9%) discontinued the treatment prior to Week 24. The main reasons were: lost to follow-up (6 subjects), withdrawal of consent (3 subjects), AEs (3 subjects), physician decision (2 subjects), death (1 subject) and other reason (1 subject). All subject who discontinued the treatment also discontinued the study, the remaining 394 (96.1%) subjects completed the study up to Week 24. From the total number of 16 discontinuations, the **AEs reason** were reported in **3 patients who discontinued the study treatment**. The patient no 160308 with detachment of retinal pigment epithelium and vitritis then discontinued the study due withdrawal consent, therefore the number of subjects who discontinued the study due AEs was only 2.

However, the following information can be obtained from the final safety evaluation (chapter 12.0, pg. 119) and safety summary: 5 subjects (1.2 %) reported TEAEs that led to the d**iscontinuation of the study treatment** – 2 (1%) from the Mynzepli arm with 2 events and 3 (1.5%) from the Eylea arm with 4 events. Of these subjects, 1 patient in the Mynzepli (1 TEAE - retinal haemorrhage) and 2 patients (3 TEAEs – detachment of retinal pigment epithelium and vitritis at the same time in one subject, IOP increased) in the Eylea group reported ocular AEs. The non-ocular TEAEs were rheumatoid arthritis in Mynzepli patient and rib fracture in Eylea patient. A total of 4 subjects (2 in each group) reported TEAE which led to **discontinuation from the study**. It was stated by the applicant that also the patient 110905 (rib fracture, death) and patient 250512 (retinal haemorrhage, the study was ended after Week 24, although the AE leading to discontinuation started prior Week 24 and the treatment administered at Week 24 was the last one) are counted here. This is acceptable.

All narratives for the above-mentioned patients can be found in the documentation. The reported AEs which led to discontinuation were assessed as not related or unlikely to be related to the study treatment, only the patient No 250512 reported (sub)retinal haemorrhage (AESI) which was judged as probably related to AVT06. Retinal haemorrhage is already listed in the SmPC of Eylea with frequency very common, therefore the occurrence of this AE is expected.

In conclusion, it is agreed that no clinically meaningful differences were seen across all treatment groups in terms of TEAEs leading to IP discontinuation.

Subgroup analysis

The included population consisted of more than 50% of the subjects being White (76.1% compared to 16.3% Asian, 6.6% Japan, and less than 1% for Black or African American, Multiple and Not reported) and from Europe (57.1% compared to 17.8% Americas, 6.8% Japan and 18.3% other). Twenty-eight

(6.8%) subjects were Japanese. The mean (SD) BCVA score and CST at baseline was 55 (12.07) letters and 433.6 (122.79) µm; 52.2% of the subjects had baseline BCVA score ≥54 letters, and 50% of the subjects had baseline CST≥400 µm. For iris colour (IWRS), 46.8% had light irides (53.2% had non-light irides). Majority (91.5%) of the subjects were ADA negative at baseline and nAb status was unavailable in 94.1% of the population, negative in 5.4% and positive in 0.5%.

No clinical meaningful differences were seen between Mynzepli and EU-Eylea regarding Geographical Origins, Race (Japanese, Non-Japanese), baseline BVCA, Iris colour and Baseline Central Subfield Thickness.

Immunogenicity

Regarding immunogenicity, in the scientific advice (EMA/SA/0000063900), it was concluded that in terms of immunogenicity assessment for the biosimilar products, the wet AMD patient population is agreed as a sensitive patient population. Although, it is uncertain whether this is the most sensitive trial population compared to other indications, notably those including younger age groups, it is however acknowledged that the proportion of patients who developed ADAs was low across all indications. Moreover, the safety profile is also similar across the indications approved for Eylea.

Information on the risk of immunogenicity is described in sections 4.4 and 4.8 of SmPC in line with the reference medicinal product. TEAEs were assessed also by ADA status resp. nAb status in patients. In the ADA positive subgroup, the incidence of subjects with treatment-emergent AESIs was comparable between treatment groups (Mynzepli: 4.1%; Eylea: 6.3%). Similarly, in the nAb positive subgroup the incidence of subjects with treatment-emergent AESIs was comparable (Eylea: 6.1% vs Mynzepli: 5%). The incidence of TEAEs, AESI or serious TEAEs was similar between both treatment arms, therefore, no impact on overall Mynzepli safety profile compared to reference product Eylea is expected.

Laboratory and other investigations.

No clinical meaningful changes in the mean values were observed from baseline to week 4, 8 and 24 for hematology, blood chemistry, urinalysis and other tests assessments except some individual cases which were assessed as TEAEs. (Most of them were non-serious TEAE, mild or moderate in severity, not related to the treatment and resolved or were resolving at the time of the analysis. No safety concerns are raised regarding clinical laboratory evaluations, vital signs, and electrocardiogram.

In the Eylea group, one patient (150201) had elevation of both GGT (78 U/L vs 101 U/L at baseline; reference range 5-36 U/L) at week 8 (60 U/L at week 4) and ALT (117 U/L vs 53 U/L at baseline; reference range 0-41 U/L) at week 24 (53 U/L at week 8). Changes in both parameters were considered as TEAEs and assessed as related to Eylea. However, causality with Eylea is questionable.

Up to week 52, mean (SD) intraocular pressure in the study eye at baseline for Mynzepli and EU-Eylea were comparable (14.6 (2.54) Mynzepli and 14.9 (2.52) EU-Eylea). Similarly, no significant differences were observed between treatment arms regarding intraocular pressure in the study eye at Day 1, Week 4, Week 8, Week 16, Week 24 and Week 52. Mean (SD) intraocular pressure in the fellow eye at baseline and Day 1 30-60 minutes post dose was comparable between Mynzepli and EU-Eylea groups. No safety concerns are raised regarding biomicroscopy and indirect ophthalmoscopy results up to week 24.

Up to week 52, there were no notable differences in mean changes from baseline in physical examination findings and no abnormal clinically significant physical examination were assessed as related to Mynzepli nor EU-Eylea arms. All TEAEs were non-serious mild or moderate and resolved or resolving. No safety concerns are raised regarding physical examination.

Special situations

No case of overdose was reported during clinical studies of AVT06, and no special investigations were performed.

The effect on ability of drive or operate machinery information, withdrawal and rebound information, drug abuse, use in pregnancy and lactation, drug interactions and effect of extrinsic factors are extrapolated from the reference product Eylea.

2.4.10. Conclusions on the clinical safety

Biosimilarity is supported by the clinical safety data presented.

2.5. Risk Management Plan

2.5.1. Safety concerns

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

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire will be used for any reports suspicious for endophthalmitis and intraocular inflammation. Additional pharmacovigilance activities: None.
Intraocular inflammation	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire will be used for any reports suspicious for endophthalmitis and intraocular inflammation. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Transient intraocular pressure increase	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 and 4.9. PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire will be used for report regarding IOP increase following the use of the Mynzepli pre-filled syringe. Additional pharmacovigilance activities: None.
Retinal pigment epithelial tears	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Cataract (especially of traumatic origin)	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PIL sections 2, 3 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	
Medication errors	Routine risk minimisation measures: SmPC sections 4.2, 4.9 and 6.6. PIL sections 1 and 3. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Off-label use and misuse	Routine risk minimisation measures: SmPC sections 4.1, 4.3, 4.4 and 4.6 PIL sections 1, 2 and 3. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Embryo- fetotoxicity	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and 5.3. PIL section 2. Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Material: Prescriber Guide (with an intravitreal injection procedure video and pictogram), Patient Guide and its audio version.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

2.5.4. Conclusion

The CHMP considers that the risk management plan version 1.1 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, Mynzepli (aflibercept) is included in the additional monitoring list as it is a biological product authorised after 1 January 20211.

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

Mynzepli was developed as a biosimilar product to Eylea (INN: aflibercept; EMEA/H/C/002392) for intravitreal injection only (pharmaceutical form: vial and pre-filled syringe).

The indications and posology proposed are the same as that of EU – EYLEA (Bayer, Germany) with exception of Retinopathy of prematurity (ROP) with zone I (stage1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP).

A rigorous and comprehensive characterization of the structure, purity, and in vitro biological activity of Mynzepli to the reference products (RP), EU-Eylea and US-Eylea was the cornerstone of the biosimilar development program and was carried out using standard and state-of-the-art methods to provide a detailed, multi-faceted comparative analytical similarity assessment.

Head-to-head (H2H) comparative analytical similarity assessments were conducted as part of Quality Target Product Profile (QTPP) assessments. It was ensured that a sufficient number of batches for analysis were available, allowing to understand variability of Mynzepli and reference product and draw valid conclusions on similarity.

A comparative forced degradation between AVT06, EU- and US-Eylea was also performed.

The non-clinical development relies on in vitro similarity studies to evaluate biological properties of Mynzepli and to demonstrate its biosimilarity to EU-, US- and CN-Eylea. Although in vivo studies are 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), several in vivo studies were conducted by the applicant in order to assess the safety of use of poloxamer 188 and to underline similarity of Mynzepli FP with Eylea.

Regarding clinical development program a single pivotal study AVT06-GL-C01 was designed to demonstrate clinical similarity between Mynzepli and Eylea. This comparative efficacy, safety, and immunogenicity study was conducted in participants with neovascular (wet) AMD to establish equivalence in efficacy of Mynzepli (vial) to EU-Eylea (PFS).

Over the course the scientific advice procedures, it was agreed that wAMD is an adequately sensitive population and therefore acceptable to evaluate potential differences between Mynzepli and Eylea for the demonstration of biosimilarity. The applicant adapted the clinical trial with regard to CHMP recommendations (study design elements, selection criteria, methodological PK, immunogenicity measurement …).

3.2. Results supporting biosimilarity

Quality

As regards the comparability exercise, the presented analytical data demonstrate analytical similarity of the proposed biosimilar AVT06-FP and the reference products EU-Eylea and US-Eylea. Minor analytical differences have been appropriately assessed by the applicant regarding their potential impact on clinical performance of the product. The observed differences are not expected to adversely impact clinical performance of AVT06-FP.

From the quality perspective AVT06-FP is considered similar to EU-Eylea and is considered approvable as proposed biosimilar to Eylea.

Non-clinical

Overall, the available nonclinical *in vitro* studies support the MAA of Mynzepli and are in compliance with legislation from EU as well as the biosimilar relevant guidance from the EMA. There are no major objections to the approval of Mynzepli from a non-clinical perspective. The design of the nonclinical *in vitro* package required for MAA of biosimilar products is considered appropriate.

Clinical

Pharmacokinetics

The low plasma concentrations of free aflibercept indicate no relevant systemic exposure and no trend for accumulation following 2 mg/0.5 mL Mynzepli IVT repeated administration according to the recommended dosing schema. Again, the very limited PK data (especially the low PK dataset) should be regarded only for descriptive purpose and render a formal comparison between treatments (Mynzepli and Eylea) futile.

Efficacy

Primary endpoint: The applicant's primary efficacy endpoint was the change from baseline to Week 8 in BCVA measured by ETDRS letter score. At week 8, the LS mean (SE) observed for change from baseline in BCVA was similar in both treatment groups (5.11 (0.677) and 4.34 (0.687) letters in Mynzepli and Eylea group, respectively). The LS mean (SE) difference in BCVA of the change from baseline between Mynzepli and Eylea at Week 8 was 0.77 (0.829) letters (90% CI of [-0.60, 2.14]; 95% CI of [-0.86, 2.40]), and was completely contained within the pre-defined equivalence margin of [−3.5 letters, 3.5 letters]. Therefore, the results show an efficacy equivalence between Mynzepli and Eylea. The sensitivity analyses performed further strengthen the demonstration of the efficacy equivalence with regard to the primary endpoint.

Secondary endpoints: mean changes from baseline in BCVA using EDTRS letter score, CST using SD-OCT, CNV using FA and color FP and absence of intra/sub-retinal fluid at the different time-points up to Week 52 were similar between the Mynzepli and Eylea EU groups for subjects in the FAS.

Safety

From a safety perspective with consideration to the type, frequency, severity, and relatedness of reported TEAEs, the incidence of AESIs, SAEs, SAEs considered related to the Mynzepli and EU-Eylea, AEs leading to study discontinuation, and deaths, Mynzepli and EU-Eylea demonstrated comparable safety profiles.

TEAE leading to study treatment discontinuation or study discontinuation were low and comparable between treatment arms.

Changes in mean values from baseline for haematology parameters, chemistry parameters, urinalysis and vital signs were comparable between the treatment groups. No safety concerns are raised regarding biomicroscopy and indirect ophthalmoscopy results up to week 52.

3.3. Uncertainties and limitations about biosimilarity

The results at week 48 are not fully within the pre-specified equivalence margins. However, it should be considered that the study is not powered with respect to change from baseline to Week 48, due to an increased variance and the multiplicity of comparisons. Secondly, the point estimates for difference between Mynzepli and Eylea do not point to a clinical relevant difference. Thirdly, other timepoints support equivalence.

Additionally, some of the subgroup analyses showed differences between MYZENPLI and the reference product Eylea. However, both lack of biological plausibility and statistical investigations (interaction tests and SEAMOS) lead to the conclusion that there is no underlying difference.

In conclusion, the uncertainties appear modest and compatible with a conclusion of biosimilarity.

3.4. Discussion on biosimilarity

Overall, the results of the analytical similarity exercise, head-to-head comparison experiments and comparison of degradation profiles support the biosimilarity claim from the quality point of view.

The pivotal clinical study AVT06-GL-C01 was adequately designed to demonstrate clinical equivalence between Mynzepli and the reference product Eylea, both in terms of efficacy (including PK and immunogenicity assessment) and safety. The selected study population, consisting of patients with nAMD, as well as primary and secondary efficacy endpoints are deemed appropriate for this biosimilarity exercise and take into account EMA' scientific advices.

Regarding the pharmacokinetics results obtained, low plasma concentrations of free aflibercept indicate no relevant systemic exposure and no trend for accumulation following 2 mg/0.5 mL Mynzepli IVT repeated administration according to the recommended dosing schema.

Regarding the immunogenicity results obtained at baseline, 24 patients were tested ADA positive (Mynzepli: 10 patients; Eylea: 14 patients) versus 82 patients in total at Week 24 (Mynzepli: 34 patients; Eylea: 48 patients). Regarding nAb, at baseline, 2 patients were tested positive, both in Eylea group, versus 39 patients in total at Week 24 (Mynzepli: 17 patients; Eylea: 22 patients).

The primary efficacy endpoint, change in BCVA from baseline to Week 8, was well within the pre-defined and accepted equivalence margin of +/- 3.5 letters, as were the results of the secondary endpoints.

Taken together, the provided safety results from study AVT06-GL-C01 tend to support the notion of similarity between Mynzepli and the reference product Eylea (aflibercept EU) through 24 Weeks. The overall safety profile of the Mynzepli corresponds to safety profile of reference product Eylea as it is stated in the product information.

3.5. Extrapolation of safety and efficacy

The analytical similarity of Mynzepli to Eylea has been satisfactorily demonstrated and no obstacles are expected for the extrapolation of safety and efficacy from the quality point of view, provided that the raised issues are addressed.

In the EU, the reference product Eylea is approved in adults for the treatment of nAMD, RVO, DME and myopic CNV and in premature babies (ROP). The clinical development program for the proposed biosimilar Mynzepli comprised a single pivotal phase 3 study (AVT06-GL-C01) to compare Mynzepli and Eylea regarding efficacy, safety, pharmacokinetics and immunogenicity in the treatment of subjects with nAMD.

Based on the common mechanism of action (binding to VEGF-A and PlGF and tyrosine kinases receptors) across all indications and comparable PK, safety, and immunogenicity profiles of aflibercept (Eylea) across the approved indications, nAMD patients can generally be considered a sensitive population for assessing similarity in clinical efficacy of aflibercept. It is considered that the findings can be extrapolated to the other sought indications in adults which are approved for Eylea (nAMD, RVO, DME and myopic CNV in adults).

3.6. Additional considerations

The reference product has a pediatric indication and a specific dosing device for the treatment of children. Mynzepli is not indicated for pediatric use. There might be a specific risk from off label use in children however this risk is estimated to be low.

3.7. Conclusions on biosimilarity and benefit risk balance

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

Mynzepli 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).

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 Mynzepli 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 Mynzepli is marketed, ophthalmological clinics where Mynzepli 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 (for adult population only)

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
- The vial and the pre-filled syringe are for single use only
- The need to expel excess volume of the syringe before injecting Mynzepli 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 Mynzepli

The patient information pack of the educational material for the adult population 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 Mynzepli
- How to prepare for Mynzepli treatment
- What are the steps following treatment with Mynzepli
- 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 Mynzepli