20 July 2023
EMA/359132/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yesafili

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006022/0000

Note

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

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List of abbreviations

Quality

ADCC	Antibody-Dependent Cellular Cytotoxicity
AET	Analytical Evaluation Threshold
AEX	Anion Exchange Chromatography
AUC	Analytical Ultracentrifugation
C1q	Complement Component 1q
CAPA	Corrective Action And Preventive Action
CCIT	Container Closure Integrity Testing
CCS	Container Closure System
CD	Circular Dichroism
CDC	Complement-Dependent Cytotoxicity
cDNA	Circular Deoxyribonucleic Acid
CE-SDS	Capillary Electrophoresis – Sodium Dodecyl Sulfate
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
cGMP	Current Good Manufacturing Practice
CHMP	Committee For Evaluation Of Human Medicinal Products
CHO	Chinese Hamster Ovary
cIEF	Capillary Isoelectric Focusing
CoA	Certificates Of Analysis
CPA	Critical Performance Attributes
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DLS	Dynamic Light Scattering
DOE	Design Of Experiment
DSC	Differential Scanning Calorimetry
EEOPCB	Extended End-Of-Production Cell Bank
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOPCB	End-Of-Production Cell Bank
ETFE	Ethylene Tetrafluoroethylene
EU	Endotoxin Unit
EU	European Union
EVA	Ethylene-Vinyl Acetate
FcRn	Neonatal Fc Receptor
FcγR	Fc Gamma Receptor
FMEA	Failure Modes And Effect Analysis
HAP	Hamster Antibody Production
HCl	Hydrochloride
HCP	Host Cell Protein
HILIC	Hydrophilic Interaction Liquid Chromatography
HMW	High Molecular Weight
HPAE-PAD	High Performance Anion Exchange Chromatography With Pulsed Amperometric Detection
HUEVEC	Human Umbilical Vein Endothelial Cells
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IF	Intrinsic Fluorescence
IgG1	Immunoglobulin G1
IPC	In-Process Control
JP	Japanese Pharmacopoeia
kDa	Kilodalton
KDR	Kinase Insert Domain Receptor/Human

KPA	Key Performance Attributes
KPP	Key Process Parameter
LC-MS	Liquid Chromatography – Mass Spectrometry
LIVCA	Limit Of In Vitro Cell Age
MAH	Marketing Authorisation Holder
MAP	Mouse Antibody Production
MCB	Master Cell Bank
MRC-5	Medical Research Council cell strain 5
MSD	Meso Scale Discovery
MVM	Minute Virus Of Mice
NeuAc	N-Acetylneuraminic Acid
NeuGc	N-Glycolylneuraminic Acid
NMT	Not More Than
NTU	Nephelometric Turbidity Unit
OOS	Out Of Specification
PC	Polycarbonate
PC	Process Characterisation
PCB	Primary Cell Bank
PCV	Porcine Circovirus
PDLs	Population Doubling Levels
Ph. Eur.	European Pharmacopoeia
PlGF-2	Placental Growth Factor 2
PPCO	Polypropylene Copolymer
PPQ	Process Performance Qualification
PRS	Primary Reference Standard
PRV	Pseudorabies Virus
PS20	Polysorbate 20
PTM	Post Translational Modification
qPCR	Quantitative Polymerase Chain Reaction
Reo-3	Reovirus Type 3
RH	Relative Humidity
RMP	Reference Medicinal Product
RNA	Ribonucleic Acid
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
SDS-PAGE	Sodium Dodecyl-Sulfate Polyacrylamide Gel Electrophoresis
SEC-HPLC	Size Exclusion Chromatography High Performance Liquid Chromatography
SEC-MALS	Size Exclusion Chromatography Coupled With Multi Angle Light Scattering
SmPC	Summary Of Product Characteristics
SPR	Surface Plasmon Resonance
SRS	Secondary Reference Standard
SSM	Small-Scale Models
TEM	Transmission Electron Microscopy
TSE	Transmissible Spongiform Encephalopathy
UF/DF	Ultrafiltration/Diafiltration
UPLCMS	Ultraperformance Liquid Chromatography With Fluorescence Detector And Mass Spectrometry
USP	United States Pharmacopoeia
UV	Ultraviolet
VCD	Viable Cell Density
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WCB	Working Cell Bank
X-MuLV	Murine Leukaemia Virus

Non-Clinical

AMD	Age-Related Macular Degeneration
ATC	Anatomical Therapeutic Chemical (classification system)
AUC0-last	Area Under the Concentration-Time Curve from the Time of Dosing to the Last Quantifiable Concentration
CHO	Chinese Hamster Ovary
Cmax	Maximum Concentration
CNV	choroidal neovascularisation
CTAD	Citrate, Theophylline, Adenosine, Dipyridamole
CV	Coefficient of Variation
DME	Diabetic Macular Edema
ELISA	Enzyme Linked Immunosorbent Assay
GLP	Good Laboratory Practice
IVT	Intravitreal Injection
JP	Japanese Pharmacopeia
kDa	Kilodaltons
LLOQ	Lower Limit of Quantification
MAA	Marketing Authorisation Application
P1GF	Placental Growth Factor
PK	Pharmacokinetic
RVO	Retinal Vein Occlusion
Tmax	Time to Reach Maximum Concentration
ULOQ	Upper Limit of Quantification
VEGF-A	Vascular Endothelial Growth Factor A
VEGFR-1	Vascular Endothelial Growth Factor Receptor 1
VEGFR-2	Vascular Endothelial Growth Factor Receptor 2

Clinical

ADA	antidrug antibodies
AE	adverse event
AMD	Age-Related Macular Degeneration
ANCOVA	analysis of covariance
APTC	Anti-Platelet Trialists' Collaboration
ATE	Arterial thromboembolic events
BCVA	best corrected visual acuity
BDR	Blinded Data Review
BLA	Biologics License Application
BRB	blood-retinal barrier
CI	confidence interval
CMC	chemistry, manufacturing control
COVID-19	coronavirus disease 2019
CRT	central retinal thickness
CRVO	central retinal vein occlusion
CSR	Clinical study report
CST	Central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
ECG	electrocardiogram
ECL	electrochemiluminescence
EMA	European Medicines Agency
EoS	End of Study
ET	early termination
ETDRS	early treatment diabetic retinopathy study
EU	European Union
FA	Fluorescein Angiography

FAS	Full analysis set
FP	Fundus Photography
GCP	good clinical practice
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOP	intra ocular pressure
IP	investigational product
iPSP	initial Pediatric Study Plan
ITT	intent to treat
LLOQ	lower limit of quantification
LOCF	Last Observation Carried Forward
MACE	Major adverse cardiovascular events
MedDRA	Medical dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
MMRM	mixed model repeated measures
NAb	neutralizing antibody
NPDR	non proliferative diabetic retinopathy
OE	ophthalmological examination
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PEDF	pigment epithelium derived factor
PK	pharmacokinetic
PlGF	placental growth factor
PP	Per-protocolPT Preferred term
RoW	Rest of the World
RPE	retinal pigmented epithelium
RVO	Retinal Vein Occlusion
SAP	statistical analysis plan
SCDRC	Sentinel Cohort Data Review Committee
SD	Standard deviation
SD-OCT	spectral domain - optical coherence tomography
SOC	System organ class
TEAE	treatment-emergent adverse event
USFDA	United States Food and Drug AdministrationVEGF Vascular endothelial growth factor
wAMD	wet Age-Related Macular Degeneration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 29 April 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Yesafili, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 October 2021.

The applicant applied for the following indication:

Yesafili is indicated for adults for the treatment of

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is

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

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

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

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

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number(s): EU/1/12/797/001-002
- Bioavailability study number(s): MYL-1701P-3001

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
15 December 2016	EMEA/H/SA/3427/1/2016/III	Dr Kerstin Wickström and Prof Andrea Laslop
14 December 2017	EMEA/H/SA/3427/1/FU/1/2017/II	Dr Ferran Torres and Dr Kerstin Wickström
29 May 2019	EMEA/H/SA/3427/1/FU/2/2019/I	Dr Kirstine Moll Harboe and Dr Kerstin Wickström

The Scientific Advice pertained to quality development, pre-clinical development and clinical development.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur: Petr Vrbata

The application was received by the EMA on	29 April 2022
The procedure started on	19 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	1 August 2022

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 August 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 August 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	05 July 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Yesafili on	20 July 2023

2. Scientific discussion

2.1. About the product

Yesafili (MYL-1701P; M710) has been developed as a biosimilar to Eylea (aflibercept). which was authorized via the Centralised Procedure in the European Union on 22-11-2012 (marketing authorization holder Bayer AG). Aflibercept is classified under the Anatomical Therapeutic Chemical (ATC) classification system as an ocular antineovascularisation agent (ATC code: S01LA05).

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration.

In Eylea, the active pharmacologic agent, aflibercept, acts as a soluble decoy receptor that binds to VEGF-A and PlGF, and thereby inhibits the binding and activation of their cognate receptors VEGFR-1 and VEGFR-2, which are expressed on the surface of endothelial cells. Activation through VEGFR-1 and VEGFR-2 is associated with neovascularization and vascular permeability, while inhibition of activation by Eylea (aflibercept) has been demonstrated to reduce both processes, with clinical benefit in the indicated disorders.

The claimed therapeutic indications are:

Yesafili 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 Applicant claims all approved indications of Eylea in the adults for the biosimilar product MYL-1701P (M710).

The indication for the treatment of retinopathy of prematurity (ROP) in preterm infants – granted to Eylea - is not claimed at the time of the submission.

2.2. Quality aspects

2.2.1. Introduction

Yesafili has been developed as biosimilar to Eylea (EMEA/H/C/002392) for intravitreal injection. The finished product is presented as solution for injection in a vial containing 40 mg/mL of aflibercept as active substance.

Other ingredients are: histidine, histidine hydrochloride monohydrate, polysorbate 20 (E 432), trehalose dihydrate and water for injections.

The product is available in a vial (type I glass) with a stopper (chlorobutyl rubber), under 2 different pack sizes: pack size containing 1 vial and a 5-micron (18 G ×1½-inch) filter needle and pack size of 1 vial, a 5-micron sterile filter needle (18 G ×1½-inch), a 1 mL Luer-lock syringe and an injection needle (30 G ×½-inch), respectively. Not all pack sizes may be marketed.

2.2.2. Active Substance

2.2.2.1. General Information

The active substance (INN: aflibercept; company code MYL-1701P or M710) is a recombinant fusion protein consisting of human vascular endothelial growth factor (VEGF) receptor-1 (VEGFR-1) and receptor-2 (VEGFR-2) extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1) and is produced in recombinant Chinese Hamster Ovary (CHO) cells. The homodimeric fusion protein consists of 431 amino acids in each chain and has a molecular mass of 115 kilodaltons (kDa) of which approximately 15% is carbohydrate; the non-glycosylated mass is 97 kDa. There are five N-glycosylation sites on each chain at asparagine-36, asparagine-68, asparagine-123, asparagine-196 and asparagine-282.

The amino acid sequence of aflibercept is shown in Figure 1. Aflibercept selectively binds both human vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF). By preventing interaction with their cognate receptors, aflibercept reduces pathological angiogenesis and prevents vascular leakage.

The general information on the active substance is considered sufficient.

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          10         20         30         40         50
SDTGRPFVEM YSEIPEIIHM TEGRELVIPC RVTSPNITVT LKKFPLDTLI
          60         70         80         90        100
PDGKRIIWDS RKGFIISNAT YKEIGLLTCE ATVNGHLYKT NYLTHRQTNT
         110        120        130        140        150
IIDVVLSPSH GIELSVGEKL VLNCTARTEL NVGIDFNWEY PSSKHQHKKL
         160        170        180        190        200
VNRDLKTQSG SEMKKFLSTL TIDGVTRSDQ GLYTCAASSG LMTKKNSTFV
         210        220        230        240        250
RVHEKDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
         260        270        280        290        300
VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
         310        320        330        340        350
GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL
         360        370        380        390        400
TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS
         410        420        430
RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
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Figure 1. Amino acid sequence of aflibercept

2.2.2.2. Manufacture, process controls and characterisation

The active substance is manufactured, tested and released at facilities that operate in accordance with Good Manufacturing Practice (GMP).

Description of manufacturing process and process controls

The active substance is manufactured using a fermentation process in a production bioreactor.

The upstream process starts with thawing of a single vial of the working cell bank (WCB). After thawing, cells are expanded under controlled conditions which includes serial sub-cultivations in shake flasks, followed by seed bioreactors and eventually production bioreactor. Upon transfer into the production bioreactor, cells are finally expanded and maintained under defined conditions prior to harvesting of the culture supernatant.

The purification process of the active substance comprises of a combination of chromatography steps,, followed by intermediate depth filtration and ultrafiltration/diafiltration (UF/DF). Dedicated, orthogonal virus clearance steps, are integrated into the purification process. Prior to filtration through a 0.2 µm filter into the active substance container closure system (CCS), trehalose dihydrate, polysorbate 20 (PS20), and histidine−HCl are added to target the final concentration of formulation buffer and to adjust the target protein concentration.

The Applicant provided a detailed description of the manufacturing process steps that is accompanied by flow charts and tables listing process parameters and in-process controls (IPCs) with their classification and acceptable ranges/acceptance criteria/action limits. There are no critical intermediates defined for the active substance manufacturing process. No reprocessing has been claimed by the Applicant.

Sufficient details on the materials, dimensions and technical drawings for the CCS have been included in the dossier.

Overall, the active substance manufacturing process has been adequately described. Information on Critical Process Parameter (CPP), Key Process Parameters (KPP), Critical Performance Attributes (CPA) and Key Performance Attributes (KPA) is included and considered acceptable.

In conclusion, the active substance manufacturing process is considered acceptable.

Control of materials

Raw materials used for cell culture, purification and formulation of the active substance are listed in the dossier, together with their quality standard (in-house specification, compliant with Ph. Eur., USP and/or JP) and their intended use. Tests and acceptance criteria are also presented for the resins and description of the cell culture media, feed solutions and materials of construction of filters, single-use culture bags and bioreactors is also provided. No human or animal derived materials are used in the active substance manufacturing process. Overall, the provided information is considered sufficient.

The information provided on origin and history of the CHO host cell line that was adapted to serum-free suspension culture and generation of the stable-transfected production cell line clone 231-B4Z2-01-C-030 is satisfactory. A two-tiered cell bank system with MCB and WCB has been established in accordance with cGMP. The cell banking system is adequately described with sufficient details on manufacture and storage of the MCB and WCB. The cell bank specifications are acceptable. A concise description of the manufacture and qualification acceptance criteria of new WCBs is available. Stability of the cell banks is monitored by periodic determination of viability and, by taking into account the available stability data for the WCB, the proposed intervals are acceptable.

The proposed limit of in vitro cell age (LIVCA) is considered acceptable.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. The analytical methods used for in-process testing are adequately described and their suitability has been demonstrated. Actions taken if limits are exceeded are specified. The IPCs and their acceptance criteria/action limits are considered adequate.

Hold times are defined for several steps of the active substance manufacturing process and are adequately justified by data from laboratory and commercial scale studies.

Process validation

A traditional approach was chosen to verify process performance at commercial scale. Prospective process verification encompassed manufacture of a sufficient number of consecutive process performance qualification (PPQ) batches at commercial scale at the intended commercial manufacturing site according to the intended commercial process.

The acceptance criteria, action limits and expected ranges for performance attributes were defined using existing process knowledge, development and manufacturing experience, risk ranking and filtering, process failure mode and effects analysis (FMEA) and process characterisation (PC) studies comprising of univariate and multivariate design of experiment (DOE) studies etc., in order to develop a control strategy as outlined in ICH Q11 and EMA/CHMP/BWP/187338/2014. The presented approach is acceptable and the classification of process parameters (PPs) and their specified ranges/limits based on their impact on the critical quality attributes (CQAs) of the active substance and/or process performance appear reasonable.

In summary, the presented process verification data demonstrate that the intended commercial manufacturing process performs consistently and delivers active substance complying with the release specifications under commercial operating conditions.

The proposed hold times are sufficiently validated under consideration of physicochemical and microbiological hold time data. Resin lifetimes and potential carry-over, and re-usability of the UF/DF membrane have been investigated.

The Applicant performed a stepwise, two-tiered extractables/leachables risk assessment. Based on the outcome of the assessment, the risk for presence of extractables/leachables arising from the active substance manufacturing process is low and potential extractable/leachables pose no risk to patient safety.

In conclusion, the active substance manufacturing process is adequately validated.

Manufacturing process development

The production clone and active substance manufacturing process were initially developed using laboratory scale bioreactors and chromatography systems considering the ranges established with reference product lots. Thereafter, the process was scaled-up to the pilot scale and then transferred to the commercial active substance manufacturing site and scaled-up once more to the proposed commercial scale.

Information on the commercial scale manufacturing process development has been provided together with a comparability assessment using orthogonal state-of-the-art analytical procedures. Taking into account that the straightforward finished product manufacturing process has no/very limited impact on the vast majority of the quality attributes and that the comprehensive analytical comparability exercise presented in 3.2.R. support comparability between the finished product batches manufactured using both active substance scales manufactured from pre-change and post-change process, it can be agreed that the active substance produced using the pre-change and post-change process are comparable.

Characterisation

The Applicant characterised physicochemical and biological properties of MYL-1701P active substance using orthogonal, state-of-the art analytical methods, revealing that the active substance has the expected structure. Method descriptions and qualification reports are provided for the characterisation methods.

2.2.2.3. Specification

The release specification for the MYL-1701P active substance includes tests for general attributes (colour, clarity, pH, osmolality), identity, quantity, purity and impurities, potency, process-related impurities, polysorbate 20 and microbiological safety (bacterial endotoxins and bioburden).

Analytical methods

The general and microbial attributes are tested according to the respective Ph. Eur. monographs. The compendial methods have been verified to demonstrate the suitability for the intended purpose. All other attributes are tested using in-house analytical methods. Method descriptions for all non-compendial analytical procedures are provided and validations are performed according to ICH Q2(R1).

Batch analysis

Batch analyses data are presented for active substance batches. In summary, the presented results demonstrate that the manufacturing process reliably delivers active substance with consistent quality.

Reference standards

The history of the primary reference standards (PRS) used throughout development of MYL-1701P active substance is adequately described.

The Applicant intends to implement a two-tiered reference standard system, with primary and secondary reference standards (SRS). A new PRS will be qualified and annually re-qualified against the existing PRS, using the same testing programme as for the current PRS. The SRSs will be manufactured from commercial active substance batches and qualified/annually re-qualified against the PRS. The Applicant's proposal for initial qualification and re-qualification of the new PRS and SRSs is acceptable.

2.2.2.4. Stability

The Applicant provided stability data. Data are available for storage at long-term storage conditions and accelerated conditions. Forced degradation studies including heat, high/low pH, oxidation and light stress were conducted using MYL-1701P active substance and finished product, which has the same composition as the active substance.

The design of the stability studies is mainly in accordance with ICH Q5C. The samples are stored in containers that are representative for the commercial CCS.

In conclusion, the presented data support the proposed active substance shelf-life when stored in the defined CCS.

Commitments to complete the currently ongoing stability studies and to perform post-approval annual stability studies are provided. The proposed protocol (including adequate handling of any confirmed OOS) is acceptable.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and Pharmaceutical Development

MYL-1701P finished product is a sterile solution for injection intended for intravitreal administration supplied in a single-use vial. The finished product is formulated at a target concentration of 40 mg/mL of active substance in histidine, trehalose dihydrate, polysorbate 20.

There are no excipients of human or animal origin, or novel excipients used for formulation of MYL-1701P finished product. All excipients are of Ph. Eur. compendial grade and are commonly used in other commercially available intravitreal biological products, at similar concentrations. There are no overages applied for MYL-1701P finished product. Compatibility between the excipients and the active substance is considered demonstrated by the long-term stability data.

The choice of the CCS has been validated by stability data and is adequate for the intended use of the product.

MYL-1701P is available in packs containing 1 vial and a 5-micron (18 G ×1½-inch) filter needle and packs containing 1 vial, a 5-micron sterile filter needle (18 G ×1½-inch), a 1 mL Luer-lock syringe and an injection needle (30 G ×½-inch). All device components are CE-marked.

2.2.3.2. Manufacture of the product and process controls

The manufacture, control, packaging and release of MYL-1701P finished product is performed, in accordance with GMP.

MYL-1701P finished product manufacturing process is performed by a standard aseptic filling process for sterile injectable preparations commonly used in production of biotechnological pharmaceuticals. It

includes thawing of the active substance, pooling and mixing, bioburden filtration, sterile filtration, aseptic filling and stoppering, capping and visual inspection.

The manufacturing process development has been described in sufficient detail. Appropriate critical process steps and IPCs are described in the dossier. The defined set of process parameters have been shown to be suitable for monitoring the manufacturing process. In addition, ranges and values chosen for the processing parameters are acceptable and support the commercial manufacture of the product. Hold times are sufficiently justified.

Finished product manufacturing process validation was performed following a classical validation approach and covered all finished product manufacturing steps.

Data supporting shipment of the finished product from the manufacturing site to the distribution site have been provided and are considered acceptable.

2.2.3.3. Product specification

The list of finished product specification includes controls of identity, purity, impurities, sterility and other general tests.

In summary, the selection of specification attributes and setting of the acceptance criteria are in line with ICH Q6B and are found adequate to control the quality of the MYL-1701P finished product.

The Applicant provided a risk assessment as per ICH Q3D guidance for the potential elemental impurities. No potential sources of Class 1, 2, or 3 elemental impurities as defined by ICH Q3D were identified and none of these elements are intentionally added during the process. In addition, a risk-based assessment was completed to determine the organic extractables and leachables present in the components of the manufacturing train. The conclusion that potential leachables arising from the manufacturing process and present in the finished product pose no risk to patient safety is found sufficiently addressed and no additional controls are necessary.

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

Analytical methods

The finished product is tested using both compendial and non-compendial methods. Many of the methods used to test the finished product are equivalent to the methods used to test the active substance. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analyses data have been provided . Results complied with pre-defined acceptance criteria for all batches. Furthermore, the provided batch data confirm consistency of the finished product manufacturing process.

Reference materials

The reference standard is the same as that used for testing of the active substance. Reference is made to the corresponding active substance section.

2.2.3.4. Stability of the product

The proposed finished product shelf-life of 36 months when stored at 2°C to 8°C is sufficiently justified based on long-term stability. This is considered adequately justified.

All stability studies have been conducted according to ICH guidelines. The container closure system used for the stability studies is the same as that used during routine manufacture and as intended for marketing.

In conclusion, the stability data demonstrate that the finished product is stable at the recommended long-term storage condition of 2°C to 8°C and stored in the original package in order to protect from light, as mentioned in the SmPC, supporting the proposed shelf-life of 36 months.

Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed OOS is proposed. Furthermore, as part of the post-approval stability commitment, one finished product batch per year will be subjected to stability testing and evaluation for continuous stability monitoring.

2.2.3.5. Adventitious agents

Multiple complementing measures are implemented to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection and testing of materials, testing of cell banks and process intermediates for microbial and viral contaminants, testing of microbial attributes as in-process controls and at release, implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction. In addition, microbial quality is ensured by process design (microbial reduction filtrations, sterile filtration, aseptic processing) and sanitisation procedures.

In summary, the risk of potential contamination and transmission of bacterial, fungal, viral or TSE agents appears acceptably low.

2.2.3.6. GMO

Not applicable.

2.2.3.7. Biosimilarity

Analytical similarity of MYL-1701P finished product was assessed in a comprehensive analytical similarity exercise using EU-sourced Eylea as reference medicinal product (RMP). The pivotal clinical Phase 3 study MYL-1701P-3001 was conducted with US-sourced Eylea and thus, the Applicant performed a three-way analytical similarity assessment between MYL-1701P, EU-Eylea and US-Eylea. The approach and methodology of the analytical similarity and comparability assessments are sufficiently described. Both comparability and similarity assessment are well presented in the dossier. Tables and figures summarising the individual results and data distribution for each parameter, chromatographs, spectra, dose-response curves etc. have been included.

Quality attributes of aflibercept were ranked (low, moderate, high and very high risk) based on a risk assessment that took into account potential impacts on clinical performance (i.e. efficacy, pharmacokinetics/pharmacodynamics, safety and immunogenicity) and the degree of uncertainty. A

summary of the criticality assignment with brief justifications for risk ranking has been provided and, in the main, the outcome of the risk assignment appears reasonable.

The Applicant used a statistical approach to evaluate comparability of MYL-1701P finished product from pilot and commercial scale and similarity of MYL-1701P and EU/US-Eylea. Under consideration of the criticality of the attribute and statistical amenability, orthogonality and sensitivity of the corresponding analytical method, attributes were either evaluated against a quality range. The Applicant's approach to evaluate comparability and similarity is not fully endorsed. While, in the main, the selection of the evaluation approach (quality range vs. qualitative assessment) appears sufficiently justified, for several attributes the Applicant's justification cannot be followed. However, taking into account that the Applicant provided graphical and/or tabular presentations of individual analytical results, as well as descriptive statistics, which enabled an assessment independent of the defined quality ranges, no concerns are raised with respect to statistical data evaluation.

The selected comprehensive set of orthogonal state-of-the–art analytical methods, which covers primary and higher order structure, size, glycoform and charge variants, post-translational modifications, protein concentration, as well as multiple biological functions mediated by the VEGF receptor domains or the Fc portion, appears adequate to address the relevant quality attributes of aflibercept. Overall, the descriptions and qualification data that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient to conclude that the analytical methods are suitable and sensitive to detect minor differences. The results show that, for many quality attributes (including multiple attributes related to the mechanism of action), MYL-1701P finished product was demonstrated to be analytically highly similar to Eylea EU. In the main, the observed differences are adequately addressed by the Applicant and are not expected to impact clinical performance of the product. In addition, analytical comparability of US-Eylea to EU-Eylea has been sufficiently demonstrated. A summary of the analytical similarity assessment between MYL-1701P finished product and EU/US-Eylea is provided in Table 1.

Table 1: Summary of analytical similarity between MYL-1701P finished product and Eylea

Quality Attribute		**Key findings**
Protein concentration by A280		Similar
Amino acid sequence		Identical
Deglycosylated Mass	Reduced mass	Similar
	Intact mass	
Conformation (Secondary & Higher Order Structure)	Melting temperature by DSC	Similar
	Structure by CD	
	Structure by IF	
	Disulfide linkage analysis	
	Free cysteine content	

Quality Attribute		Key findings
Size variants	Aggregates by SEC-HPLC	Comparable profiles.
	Monomer by SEC-HPLC	
	Aggregates by DLS	Overall comparable
	Purity by CE-SDS Reduced	Similar profiles with minor differences in peak distributions. Differences are not expected to impact clinical performance.
	Fragments by CE-SDS Reduced	
	Purity by CE-SDS Non-Reduced	Similar profiles with minor differences in peak distributions Differences are not expected to impact clinical performance.
	Fragments by CE-SDS Non-Reduced	
	Size analysis by AUC	Slightly higher sedimentation coefficient S for MYL-1701PNot expected to impact clinical performance.
	Size analysis by SEC-MALS	Higher molecular weight for HMW (and monomer) determined for MYL-1701P. Not expected to impact clinical performance.
Glycoform variants	Sialic Acid content by HPAE-PAD	Similar
	Site Specific Glycan Sialylation	MYL-1701P has higher sialylation. Sialylation distributions may affect the charge profile, but does not affect functional assays (except for galectin-1) and product efficacy.
	Site Specific Glycan High Mannose	Similar
	Site Specific Glycan Aglycosylation	MYL-1701P aglycosylation is higher compared to Eylea. Does not affect any functional assays and efficacy.
	Site Specific Glycan Fucosylation	Slightly higher and lower fucosylation for MYL-1701P. does not impact safety or efficacy of MYL-1701P.
	Galactose-α-galactose	Similar
	Site Specific Glycan Galactosylation	Higher galactosylation observed for MYL-1701P. Not expected to impact clinical performance.
	Glycoform Variants Released N-glycans by HILIC	Slightly higher fucosylation and galactosylation for MYL-1701P. No impact on clinical performance expected.
Charge variants	Charge by cIEF	Comparable pattern with differences these differences are not expected to impact clinical performance.
	Charge by cIEF (desialylated)	Similar pattern with slight differences in distribution of main and basic peak. Can be attributed to terminal lysine and other PTMs. No impact on clinical performance expected.
	Charge by AEX (desialylated)	Similar pattern with slight differences in distribution of acidic, main and basic peaks. No impact on clinical performance expected.
Post Translational Modifications (PTM)	N & C terminal variants	C-terminal lysine and amidated proline content is lower for MYL-1701P than for Eylea. No impact on clinical performance.
	Succinimide	Similar

Quality Attribute		Key findings
	Oxidation	MYL-1701P Methionine oxidation is slightly lower for MYL-1701P. Not impactful for product safety and efficacy.
	Deamidation	Slightly lower levels for MYL-1701P. No impact on clinical performance expected.
	Isoaspartic acid	MYL-1701P Isoasp is lower than Eylea. No impact on product safety and efficacy due to lower PTM.
	Isoaspartic acid (IsoQuant)	Isoaspartate is lower in MYL-1701P samples compared to RPP samples. No impact on product safety and efficacy.
VEGF-A_{165} related activity	Binding to VEGF-A_{165}	ELISA shows rather high variability. SPR reveals similar K_D values for Yesafili and Eylea.
	Potency (Inhibition of VEGF-A_{165} induced KDR dimerization)	Some MYL-1701P batches were above the narrow US Eylea quality range. All MYL-1701P lots fell within the EU Eylea range. Observation is not confirmed by other methods addressing VEGF-A binding.
	Inhibition of VEGF-A_{165} binding to VEGFR-2	Few batches were observed outside the quality range; however, the difference is small and not confirmed by more relevant cell-based potency assays.
	Inhibition VEGF-A_{165} induced cell proliferation (HUVEC)	Similar
	Inhibition of VEGF-A_{165} binding to VEGFR1	Slight trend towards higher activity for MYL-1701P. However, results are within range for EU Eylea.
Binding to other VEGF-A isoforms	Binding to VEGF-A_{121} ELISA	Rather high variability observed. When measured by SPR, binding to VEGF-A_{121} by the same batches is similar with 100% of MYL-1701P batches within Eylea US and EU quality ranges.
	Binding to VEGF-A_{121} SPR	Comparable K_D values for MYL-1701P and Eylea.
	Binding to VEGF-A_{110}	Rather high variability observed for ELISA. Binding to VEGF-A_{189} (SPR) shows comparable K_D for MYL-1701P and Eylea.
	Binding to VEGF-A_{189}	
	Binding to VEGF-A_{206}	
Binding to other VEGF isoforms	Binding to VEGF-B_{167}	Data of few lots of Yesafili observed outside the range of EU Eylea or US-licensed Eylea. VEGFB is not the main binder to the receptors. The differences are not considered significant.
	Binding to VEGF-C	No binding observed for MYL-1701P and Eylea.
	Binding to VEGF-D	
Binding to other factors	Inhibition of PlGF-2 binding to VEGFR-1	Rather high variability for US Eylea and MYL-1701P.
	Binding to Galectin-1	Compared to Eylea, binding activity of MYL-1701P is generally lower. Observed differences can be linked to glycosylation differences in R2 domain of aflibercept. This difference is rather small and clinical data from study MYL-1701P-3001 demonstrate similar efficacy of Eylea and MYL-1701P.
Binding to Fc region of the aflibercept	FcγRI binding	Similar
	FcγRIIa-H-H131 binding	Similar

Quality Attribute		Key findings
	FcγRIIa-R-H131 binding	Similar
	FcγRIIb binding	Difference is marginal.
	FcγRIIIa- V158 binding	Weaker binding activity of MYL-1701P to receptor compared to Eylea. No impact on clinical performance as aflibercept does not have effector function activity.
Binding to Fc region of the aflibercept	FcγRIIIb binding	Weaker binding of MYL-1701P to receptor compared to Eylea No impact on clinical performance as aflibercept does not have effector function activity.
	C1q Binding	Similar
	FcRn binding	Comparable data distribution with rather high variability.
Fc Effector function	Lack of ADCC	Similar
	Lack of CDC	

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

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. A comprehensive analytical biosimilarity exercise was conducted and demonstrated that, from a quality perspective, MYL-1701P was shown to be highly similar to the EU reference medicinal product (Eylea). Any observed analytical differences have been adequately justified and are not expected have a relevant impact on clinical performance of the product.

The Applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

One Major Objection was raised during the assessment due to the insufficient information regarding process characterisation studies and small-scale models and their qualification used for the purification process, which has been adequately addressed by the end of the procedure.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the request for implementation of a qualitative control of the glycan profile at release of the active substance to ensure batch-to-batch consistency of the glycan profile before the first commercial scale batch is released (Recommendation 1).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

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 recommends the following points for investigation:

1. A qualitative control of the glycan profile at release of the active substance should be implemented to ensure batch-to-batch consistency of the glycan profile before the first commercial scale batch is released.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive battery of in vitro pharmacodynamics characterization studies was performed in a side-by-side comparative manner to evaluate the key biological activities of MYL-1701P drug product (DP), EU-, US- and JP-Eylea.

2.3.2. Pharmacology

No ***in vivo*** **pharmacodynamics studies** were performed under the assumption that the biosimilar comparability exercise for the physicochemical and biological characteristics and the non-clinical *in vitro* studies are considered satisfactory. This approach is in line with the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1).

2.3.2.1. Primary pharmacodynamic studies

As VEGF-A_{165} is the primary VEGF-A isoform responsible for VEGF-mediated biological activity, the binding activity of MYL-1701P and its comparators (Eylea sourced from EU, US, and Japan) were characterized by both enzyme-linked immune-sorbent assay (ELISA) and surface plasmon resonance (SPR)-based binding kinetic method. These assays were performed as well for VEGF-A isoforms VEGF-A_{121} and VEGF-A_{189}, whereas for VEGF-A_{110} and VEGF-A_{206}, only the ELISA-based method was used. Binding affinity of MYL-1701P to VEGF-A_{165}, A_{189}, A_{110} and A_{206} was highly similar compared to all Eylea products, only two out of the seven MYL-1701P lots were outside the lower limit of quality range of US-Eylea in VEGF-A_{121} binding (see section 2.3.6 on an assessment on this). SPR binding kinetics and affinity data of MYL-1701P to VEGF-A_{165} fit within the quality range of all three comparators. No or only slight or marginal differences for values of association (k_a), dissociation (k_d) rate constants and equilibrium dissociation constants (K_D) were detected for MYL-1701P binding to VEGF-A_{121} and VEGF-A_{189} isoforms.

VEGF-B isoforms VEGF-B_{167} and VEGF-B_{186} play a partial role in angiogenesis. According to literature VEGF-B_{167} is the predominant isoform expressed in animal eyes and under the assumption that comparable angiogenic activity has been demonstrated, VEGF-B_{167} was selected as the binding target to identify any differences in VEGF-B-related biological activity between MYL-1701P and Eylea. Marginal differences in VEGF-B_{167} binding between MYL-1701P and its three comparators, Eylea sourced from EU, US and Japan, were observed but considered to be related to assay variability and accounted to an invariably limited number of lots tested.

As aflibercept is a fusion protein with the binding domains for VEGFR-1 and VEGFR-2, but not VEGFR-3, it was expected to have no binding affinity with VEGF-C and VEGF-D, which bind primarily to VEGFR-3.

Binding of VEGF-C and VEGF-D was assessed by a negative ELISA assay and the "no binding activity" was confirmed for MYL-1701P DP and for the Eylea reference products.

An SPR-based comparative assessment of binding kinetics to galectin-1, an angiogenic factor associated with proliferative diabetic retinopathy through VEGFR-2 signalling, was performed. The relative binding of Galectin-1 to MYL-1701P was within the quality range of the EU reference product though a slightly lower binding affinity was observed for MYL-1701P when compared to Eylea from US and Japan.

The primary mechanism of action for aflibercept-associated pharmacological activity, the relative inhibitory activity of MYL-1701P against VEGF-A_{165} binding to VEGFR-1 and VEGFR-2, was compared side-by-side with Eylea reference products using an electrochemiluminescent competitive ELISA-based method. Two out of five MYL-1701P GMP lots were above the upper quality range of Eylea products for the inhibition of VEGFR-2 binding (see section 2.3.6 for discussion). In regard to VEGFR-1 binding all lots of MYL-1701P stayed within the quality range of EU- and US-Eylea.

Placental growth factor (PlGF) consists of 4 major splice isoforms, PlGF-1, PlGF-2, PlGF-3, and PlGF-4, which are angiogenic factors known to bind to VEGFR-1, but not VEGFR-2. Furthermore, PlGF-1 and PlGF-3 are non-heparin binding diffusible isoforms while PlGF-2 and -4 have additional heparin binding domains (Del Falco 2012). Because PlGF-2 showed to have a more robust binding affinity to aflibercept (~10-fold) when compared with PlGF-1 (Eylea SBA 2011), PlGF-2 was used to investigate the potential of MYL-1701P to inhibit PlGF binding to VEGFR-1. An electrochemiluminescent competitive binding assay (ELISA) to determine the % relative of activity of PlGF-2 binding to VEGFR-1 in the presence of (multiple concentrations of) MYL-1701P was performed. High similarity between MYL-1701P and its comparators was observed, with only one lot of MYL-1701P above the quality range of its EU reference product (see section 2.3.6 for an assessment on this).

Binding of VEGF to the VEGFR-2 leads to dimerization of the receptor, leading to VEGF-mediated biological activity. Inhibition of VEGF-A_{165} induced KDR dimerization, as well as functional inhibition of VEGF-$_{165}$ induced HUVEC proliferation, a main step in angiogenesis was comparatively assessed for MYL-1701P and Eylea sourced from EU, US and Japan. Neither differences between any Aflibercepts were detected in the HUVEC proliferation assay, nor for MYL-1701P and EU Eylea in the KDR dimerization assay. The latter method showing some differences between MYL-1701P and Eylea from US and Japan but considered due to method variability. Please also see section 2.3.6.

No preclinical in vivo pharmacodynamics studies were conducted.

2.3.2.2. Secondary pharmacodynamic studies

A series of secondary pharmacodynamic assays were designed to investigate the MYL-1701P binding activity to the Fc receptors (including FcγR1, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, FcRn, and C1q). For each Fc receptor, a SPR-based assay was performed on a Biacore instrument platform to determine the absolute equilibrium dissociation constant (KD) (calculated for FcγRIIa R_{131}, FcγRIIa H_{131}, FcγRIIb and FcγRIIIb) or relative binding activity (for FcγRIa, FcγRIIIa V_{158}, and FcRn) of MYL-1701P or Eylea reference products to a common reference standard.

FcγR functions either as activating receptor (FcγRI, FcγRIIa, FcγRIII) or inhibitory receptor (FcγRIIb), to elicit or inhibit immune functions. Aflibercept's mechanism of action is not known to involve Fcγ receptors, nevertheless the binding to these receptors was investigated for a complete similarity assessment. A similar binding affinity was observed for FcγRI and FcγRIIa R_{131}/H_{131} (with K_d values slightly above the reference products for R_{131}), whereas binding affinities to FcγRIIb, FcγRIIIa and FcγRIIIb were found to be slightly lower for MYL-1701P, likely to be related to the slightly higher

fucosylation percentage in the Fc region of MYL-1701P and not considered to be clinically meaningful due to Aflibercept's lack of effector function associated with FcγR binding.

The FcRn receptor is known to play an important role in antibody pharmacokinetics. The relative binding affinity to FcRn of MYL-1701P was well within the quality range of its EU reference product, showing some minor differences compared to US and JP sourced Eylea.

A direct ELISA assay was performed to comparatively assess the relative binding activity of C1q, a complement protein involved in CDC, to MYL-1701P, EU-, US-, and JP-Eylea. High similarity was observed for MYL-1701P compared to its reference products.

In addition, effector functions related to FcγR and C1q binding, such as antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) were also compared between MYL-1701P and Eylea. As expected, significant ADCC and CDC activities were only observed in the corresponding positive controls, no ADCC or CDC activity was detected for MYL-1701P and Eylea sourced from EU, US and Japan.

No preclinical in vivo secondary pharmacodynamics studies were conducted.

2.3.2.3. Safety pharmacology programme

No non-clinical safety pharmacology studies were conducted.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies were conducted.

2.3.3. Pharmacokinetics

No separate absorption, distribution, metabolism, excretion, or PK drug interaction studies were conducted for MYL-1701P. A comparative single dose PK study was performed due to expectations from regulatory bodies competent for non-European regions. This study demonstrated high similarity in both systemic and ocular disposition of MYL-1701P and JP-Eylea following a single IVT injection in male Dutch Belted rabbits.

Anyway, as stated in the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" [EMA/CHMP/BMWP/403543/2010]: If the comparability exercise in the *in vitro* studies is considered satisfactory and no factors of concern are identified, or these factors of concern do not block direct entrance into humans, an *in vivo* animal study may not be considered necessary. The similarity between the originator and the biosimilar product is in the first place assessed with quality testing and *in vitro* data. In contrast to the *in vitro* methods, *in vivo* studies in animals are not considered informative for the similarity/comparability exercise. These models are considered highly variable and are actually also too insensitive. This conclusion concerns both pharmacokinetic comparisons and comparisons on safety.

Based on these considerations, these comparative studies in animal models have been discouraged. Data on ADA from animals are not predictive for the clinical situation, and comparative data on ADA are of uncertain relevance. Potential differences in immunogenicity between Aflibercept Viatris and Eylea need however to be evaluated in the clinical setup. Therefore, these *in vivo* studies can at most be considered supportive, but not as evidence of true similarity.

2.3.4. Toxicology

The applicant did not conduct non-clinical toxicology studies with MYL-1701P. Indeed, a complete package of similarity data were collected in a sensitive and comprehensive battery of in vitro studies (please also refer to the quality section), demonstrating a low risk of potential differences in non-clinical efficacy, PK, and non-immunogenicity-related general toxicity between MYL-1701P and Eylea reference product. It is a known fact that *in vivo* studies are less sensitive compared to *in vitro* biological assays in the identification of potential differences between products, and thereby also between MYL-1701P and Eylea. Another obvious reason for not conducting toxicity studies with MYL-1701P was the access to the Cynomolgus monkey toxicity studies performed with the Eylea aflibercept (Eylea EPAR 2012, Eylea SBA 2011). Only minimal systemic or local toxicities were observed after intravitreal injection of 4 mg/eye of the comparator Eylea aflibercept to the monkeys, for up to 8 months.

According to the EMEA/CHMP/BMWP/42832/2005 Rev1 guidelines, studies regarding toxicology (including developmental and reproductive toxicity studies), are not required for non-clinical testing of biosimilars. Furthermore, studies regarding safety pharmacology, carcinogenicity and local tolerance are likewise not required for non-clinical testing of biosimilars.

As such, the Applicant's approach is considered appropriate.

2.3.5. Ecotoxicity/environmental risk assessment

In accordance with Article 8(3) of Directive 2001/83/EC, as amended, the evaluation of the potential environmental risks posed by medicinal products should be submitted, their environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit the impact should be considered (Guideline on the environmental risk assessment of medicinal product for human use (EMEA/CHMP/SWP/4447/00 corr 2).

Further it is stated, that "In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment."

The Applicant provided a valid justification (as per Guideline above) for the absence of an Environmental Risk Assessment, which is deemed acceptable.

2.3.6. Discussion on non-clinical aspects

Pharmacodynamic

In vitro pharmacodynamic characterization studies were performed in a side-by-side comparative manner to match the key biological activities of MYL-1701P drug product with its referenced medicinal product (RMP) Eylea sourced from EU, US and Japan. Primary pharmacodynamic studies were conducted to evaluate concentration-activity relationships and included the following assays: binding to the VEGFR-1 and -2 target ligands (VEGF-A110, VEGF-A121, VEGF-A165, VEGF-A189, VEGF-A206, VEGF-B167, VEGF-C, VEGF-D, and Galectin-1), inhibition of VEGF-A165-binding to VEGFR-1 and VEGFR-2, inhibition of VEGF-A165-induced VEGFR-2 dimerization, inhibition of PlGF-2 binding with VEGFR-1, and functional inhibition of VEGF induced proliferation of human umbilical vein endothelial cells (HUVEC). Although Aflibercept's mechanism of action is not known to involve Fcγ receptors, a comprehensive battery of secondary pharmacodynamic assays was performed, including binding activity of MYL-1701P to the Fc receptors as follows: FcγR1, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, FcRn, and C1q. Additionally, antibody

dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) assays were also included as part of the similarity exercise.

No *in vivo* animal studies were conducted in addition to the analytical biosimilarity assessment, investigating analytical, physiochemical and functional similarity between MYL-1701P and its RMP Eylea, sourced from EU , US and Japan. This is accepted because, as outlined in the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014) and the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1), a stepwise approach is recommended for evaluation of the biosimilarity of drug product (DP) and the EU-licenced referenced medicinal product (RMP). *In vitro* assays are considered as paramount for the non-clinical biosimilar comparability exercise since they are considered more specific and sensitive in detecting differences between the biosimilar and the RMP.

No concerns are raised from the pharmacology point of perspective. Please follow the Quality Assessment report regarding the comparability assessment.

Pharmacokinetics

"A comparative single dose PK study was performed due to expectations from regulatory bodies competent for non-European regions. No other pharmacokinetics studies were conducted with MYL 1701P.

It is acknowledged, that the *in vivo* studies were conducted due to expectations from regulatory bodies competent for non-European regions. Generally, the European guidance on biosimilar development provides sufficient flexibility to acknowledge aspects of a globalized development program. Though not requested, results of these *in vivo* testings are accepted and are in support of the MAA of Aflibercept Viatris. Ultimately, clinical data supersede and should address any potential PK and immunogenicity differences (including different excipients used) between the products.

Toxicology & Environmental Risk Assessment

The applicant did not conduct non-clinical toxicology studies with MYL-1701P. Due to the EMEA/CHMP/BMWP/42832/2005 Rev1 guidelines, studies regarding toxicology (including developmental and reproductive toxicity studies), are not required for non-clinical testing of biosimilars. Furthermore, studies regarding safety pharmacology, carcinogenicity and local tolerance are likewise not required for non-clinical testing of biosimilars. The Applicant’s approach is considered appropriate.

Aflibercept is already used in existing marketed products (Eylea) and no significant increase in environmental exposure is anticipated. Therefore, Aflibercept Viatris is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

Not applicable.

2.3.7. Conclusion on the non-clinical aspects

In line with the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1), no ***in vivo* pharmacodynamics studies** were performed under the assumption that the biosimilar comparability exercise for the physicochemical and biological characteristics and the non-clinical *in vitro* studies are considered satisfactory.

Overall, the comprehensive ***in vitro*** **biosimilarity exercise** provided by the Applicant is considered to be sufficiently sensitive and discriminatory to detect potential differences between the biosimilar candidate MYL-1701P and its comparators EU-, US- and JP-Eylea. For a thorough assessment, please refer to the discussion and conclusion of the quality section.

No non-clinical **safety pharmacology** studies were conducted which is accepted, as they are not required for the non-clinical testing of biosimilars according to the same guideline as cited above.

Furthermore, no **pharmacodynamics drug-drug interaction** studies were conducted for MYL-1701P, which is acceptable.

Following the general requirements for Article 10(4) application from non-clinical perspective, sufficient data has been provided. Studies on **genotoxic** and **carcinogenic potential** as well as **for reproductive toxicology and local tolerance** are not required for biosimilars.

Studies with originator have shown **embryo-foetal toxicity** and results from studies in monkeys with high systemic exposure indicate that aflibercept can impair male and female fertility.

Proposed SmPC is in accordance with the PI for Eylea (10/02/2022, EMEA/H/C/002392 - II/0078).

Overall, from a non-clinical perspective, no major concerns have been raised. There are no objections to authorisation of this medicinal product.

2.4. Clinical aspects

- **Tabular overview of clinical studies**

Type of Study	Study Number	Study Objective(s)	Study Design	Test Product(s), Dosage, Regimen, Route of Administration	Number of Subjects/ Diagnosis	Duration of Treatment	Study Status; Type of Report; Location
Pivotal Studies							
Comparative efficacy, safety, and immunogenicity	MYL-1701P-3001	**Primary:** • The primary objective was to evaluate the clinical equivalence of MYL-1701P and Eylea over 8 weeks of treatment at doses and regimen recommended by the Prescribing Information for Eylea, as assessed by change from baseline to Week 8 in BCVA **Secondary:** The key secondary objective of this study was: • To compare the efficacy of MYL-1701P and Eylea as measured by change in central retinal thickness (CRT) over time The other secondary objectives were: • To compare the efficacy of MYL-1701P and Eylea as measured by change in BCVA over time • To compare safety, tolerability, pharmacokinetics, and immunogenicity over time of MYL-1701P and Eylea • To compare the number of administrations of study drug required over the treatment period • To compare impact of immunogenicity on efficacy and safety	Multi Center, Randomized, Double Masked, Active Controlled, Comparative Clinical Study	MYL-1701P or Eylea, an intravitreal injection at a dose of 2 mg every 4 weeks for a total of 5 injections, and then every 8 weeks through the remainder of the 52-week treatment period, with the last dose at 48 weeks	355 Patients with type 1 or type 2 diabetes mellitus who present with central DME involvement	Week 52 - final clinical study report	Completed (Module5.3.5.1)

2.4.1. Clinical pharmacology

2.4.1.1. Pharmacokinetics

No dedicated Phase I human PK study was conducted for MYL-1701P. Instead, supportive PK analyses were conducted in a subset of patients enrolled in MYL-1701P-3001, which was acceptable, since systemic exposure after intravitreal injection is expected to be low, and due to ethical considerations.

Analytical Methods

PK ELISA

The ELISA used for quantification of Aflibercept (MYL-1701P and Eylea) in human CTAD plasma has been validated in line with the GL on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). The assays ability to quantitate both Eylea and MYL-1701P in CTAD plasma using a single assay approach (standards prepared only with the biosimilar) has been sufficiently demonstrated. The method is linear within the range of 15.0 ng/mL (LLOQ) and 400 ng/mL (ULOQ). Performance of the assay during clinical study MYL-1701P-3001 is considered acceptable. The Applicant confirmed dilution linearity of study samples. Overall, the PK ELISA for quantification of Aflibercept in CTAD plasma (method 19-002) can be considered as suitable for its intended purpose.

Bioequivalence

Clinical study MYL-1701P-3001 was conducted to evaluate the clinical similarity of MYL-1701P and Eylea with regards to efficacy, safety, pharmacokinetics and immunogenicity in the treatment of subjects with DME. Supportive PK analyses were conducted in a subset of patients enrolled in MYL-1701P-3001.

At least 32 subjects in each study arm were planned to be included in the PK subset. This target has been met for both relevant time points: 41 and 37 subjects (MYL-1701P), and 44 and 38 subjects (Eylea) were assessed at V2 (2 days after the first injection) and V7A (2 days after the 5th injection), respectively.

Subjects included in the PK subset comprised patients agreeing to participate also to PK sampling. The patients enrolled under this PK sub-study had a separate stratification at the IWRS level to ensure equal distribution among the treatment groups. The Applicant presented demographics, general baseline data and disease characteristics for the PK subset for both treatment groups upon request. The demographic profiles and baseline characteristics of the PK subset were largely comparable between the treatment groups. More males were included in the PK subset of the Eylea arm compared to MYL-1701P (63.8% vs 54.8%), which might suggest a higher body weight in the Eylea group. Conversely, the mean body weight was even lower in the Eylea group (82.6 kg vs 85.3 kg MYL-1701P) and more obese subjects (BMI >30) were included in the MYL-1701P group (54.8% vs 31.9% Eylea), which may have an impact of systemic drug exposure. However, despite these imbalances in baseline data for the PK subset, no concern is raised, as systemic exposure of aflibercept after intravitreal injection is generally low and interpretable results indicated similarity between the treatment groups (see below). For all the subjects in the PK subpopulation, concentrations of aflibercept (free drug) are summarized at each scheduled sampling time (Table 2). Most of the plasma concentrations across all visits were below the LLOQ (BLQ) in both the treatment arms. Peak plasma concentrations were observed post-dose at Day 2 (both at Visit 2 and Visit 7A). The mean plasma concentrations at Day 2 after first dose were 25.2 ng/mL in MYL-1701P arm and 27.6 ng/mL in Eylea arm. The mean plasma concentrations at Day 2 after the 5th dose were 34.4 ng/mL in MYL-1701P and 30.8 ng/mL in the Eylea arm. In general, the mean values for plasma concentrations were similar in both arms at corresponding time points. Even at time points with peak plasma concentrations, a large proportion of

subjects in both arms had BLQ plasma concentrations. It is critically noted that observed mean values are not far above the LLOQ (15.0 ng/mL), which in principle could hamper the interpretation of results. However, as systemic exposure to aflibercept after intravitreal injection was expected to be low, and indeed the results do confirm this for both treatment arms, this is acceptable. There was no sign of accumulation of free aflibercept after repeated intravitreal dosing.

At V2 (2 days after the first injection), no considerable differences were observed between ADA positive and ADA negative subjects. At V7A (2 days after 5th injection), ADA positive subjects had lower mean free aflibercept values compared to ADA negative subjects, while the opposite was observed in the Eylea arm. However, only 2 patients in the MYL-1701P arm and 4 patients in the Eylea arm were ADA positive at both time points, and this observation is considered a random finding. No conclusion from these patients is possible and this observation does not raise any further concerns.

Table 2: Summary of Aflibercept (Free Drug) Concentration (ng/ml) -PK Sub-Set

		Visit											
Population	Summary Statistic	V 1 (D1)	V 2# (D3)	V 3# (W1)	V 4 (W4)	V 5 (W8)	V 7 (W16)	V 7A# (2 days postV7)	V 9 (W24)	V 11 (W32)	V 13 (W40)	V 16 (W52)	EOT / EOS
MYL-1701P (N=42)													
All	n	41	41	38	40	41	41	37	38	35	39	39	39
	n*	41	9	26	39	40	41	8	38	35	39	39	39
	Mean	0.000	25.218	7.284	0.461	0.410	0.000	34.355	0.000	0.000	0.000	0.000	0.000
	SD	0.0000	23.7111	12.1834	2.9140	2.6268	0.0000	30.6935	0.0000	0.0000	0.0000	0.0000	0.0000
	Median	0.000	21.470	0.000	0.000	0.000	0.000	29.350	0.000	0.000	0.000	0.000	0.000
	Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Maximum	0.00	108.40	47.36	18.43	16.82	0.00	107.50	0.00	0.00	0.00	0.00	0.00
ADA Positive	n	2	2	2	2	2	2	2	2	2	2	2	2
	n*	2	0	2	2	2	2	0	2	2	2	2	2
	Mean	0.000	21.760	0.000	0.000	0.000	0.000	19.190	0.000	0.000	0.000	0.000	0.000
	SD	0.0000	5.1619	0.0000	0.0000	0.0000	0.0000	2.4042	0.0000	0.0000	0.0000	0.0000	0.0000
	Median	0.000	21.760	0.000	0.000	0.000	0.000	19.190	0.000	0.000	0.000	0.000	0.000
	Minimum	0.00	18.11	0.00	0.00	0.00	0.00	17.49	0.00	0.00	0.00	0.00	0.00
	Maximum	0.00	25.41	0.00	0.00	0.00	0.00	20.89	0.00	0.00	0.00	0.00	0.00
ADA Negative	n	39	39	36	38	39	39	35	36	33	37	37	37
	n*	39	9	24	37	38	39	8	36	33	37	37	37
	Mean	0.000	25.395	7.688	0.485	0.431	0.000	35.221	0.000	0.000	0.000	0.000	0.000
	SD	0.0000	24.2991	12.3982	2.9897	2.6934	0.0000	31.3535	0.0000	0.0000	0.0000	0.0000	0.0000
	Median	0.000	21.470	0.000	0.000	0.000	0.000	29.980	0.000	0.000	0.000	0.000	0.000
	Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Maximum	0.00	108.40	47.36	18.43	16.82	0.00	107.50	0.00	0.00	0.00	0.00	0.00
Eylea (N=47)													
All	n	47	44	47	46	45	43	38	44	41	43	39	39
	n*	47	16	34	45	43	42	8	44	41	42	39	39
	Mean	0.000	27.567	9.570	0.412	0.861	0.384	30.758	0.000	0.000	0.491	0.000	0.000
	SD	0.0000	40.6477	19.0000	2.7970	4.0931	2.5193	32.3208	0.0000	0.0000	3.2177	0.0000	0.0000
	Median	0.000	18.410	0.000	0.000	0.000	0.000	21.705	0.000	0.000	0.000	0.000	0.000
	Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Maximum	0.00	244.30	89.55	18.97	22.54	16.52	138.70	0.00	0.00	21.10	0.00	0.00
ADA Positive	n	4	4	4	4	4	4	4	3	4	3	3	3
	n*	4	1	4	4	4	4	2	3	4	3	3	3
	Mean	0.000	21.585	0.000	0.000	0.000	0.000	52.665	0.000	0.000	0.000	0.000	0.000
	SD	0.0000	15.4814	0.0000	0.0000	0.0000	0.0000	66.6371	0.0000	0.0000	0.0000	0.0000	0.0000
	Median	0.000	26.305	0.000	0.000	0.000	0.000	35.980	0.000	0.000	0.000	0.000	0.000
	Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Maximum	0.00	33.73	0.00	0.00	0.00	0.00	138.70	0.00	0.00	0.00	0.00	0.00
ADA Negative	n	43	40	43	42	41	39	34	41	37	40	36	36
	n*	43	15	30	41	39	38	6	41	37	39	36	36
	Mean	0.000	28.166	10.460	0.452	0.945	0.424	28.181	0.000	0.000	0.528	0.000	0.000
	SD	0.0000	42.4172	19.6430	2.9271	4.2834	2.6453	26.5058	0.0000	0.0000	3.3362	0.0000	0.0000
	Median	0.000	17.550	0.000	0.000	0.000	0.000	21.705	0.000	0.000	0.000	0.000	0.000
	Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Maximum	0.00	244.30	89.55	18.97	22.54	16.52	107.60	0.00	0.00	21.10	0.00	0.00

n=number of subjects in the specified category with non-missing values; N=number of subjects in the treatment group analysis set. n*=number of subjects with concentrations below the lower limit of quantification. ADA positive means positive at any time up to Week 52. # Samples collected at post-dose timepoints, samples at all other timepoints were collected prior to the study drug administration at the respective visits. D=Day; W=Week.

Source: Table 14.6b and Listing 16.2.9.5b.

2.4.1.2. Pharmacodynamics

Mechanism of action

Eylea is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration.

The active pharmacologic agent, in Eylea (aflibercept), acts as a soluble decoy receptor that binds to VEGF-A and PlGF, and thereby inhibits the binding and activation of their cognate receptors VEGFR-1 and VEGFR-2, which are expressed on the surface of endothelial cells. Activation through VEGFR-1 and VEGFR-2 is associated with neovascularization and vascular permeability, while inhibition of activation by Eylea (aflibercept) has been demonstrated to reduce both processes, with clinical benefit in the indicated disorders.

The mechanism of action is described sufficiently.

Primary and Secondary pharmacology

No clinical comparative PD studies have been performed with MYL-1701P.

In clinical study MYL-1701P-3001 central retinal thickness (CRT) over time determined by SD-OCT was included as key secondary endpoint to reflect PD aspects of aflibercept. Lesion characteristics such as presence of leakage or hemorrhage were evaluated using fundus photography (FP) and/or fluorescein angiography (FA).

2.4.2. Discussion on clinical pharmacology

Pharmacokinetics: The PK profiles of MYL-1701P and US-Eylea were compared in a subset of patients enrolled in clinical Phase III study (MYL-1701P-3001) to support a comparative evaluation between the two products.

Based on the comprehensive quality- and non-clinical bridging exercise, the use of an US-approved reference product is accepted.

Systemic exposure of aflibercept after intravitreal injection is expected to be low. It was therefore acceptable that PK would be assessed in a subset of DME patients only. It was agreed that comparative PK assessment of free aflibercept around the expected maximum systemic exposure would be considered appropriate and supportive only. No formal hypothesis testing was planned for, and at least 32 subjects in each study arm were planned to be included in the PK subset, which is accepted. This target has been met for both investigated PK time points: 41 and 37 subjects (MYL-1701P), and 44 and 38 subjects (Eylea) were assessed at V2 (anticipated Tmax) and V7A (anticipated Cmax at steady state), respectively.

As expected, interpretable results were only observed 2 days after the first injection (V2) and 2 days after the 5th injection (V7A), and most of the plasma concentrations across all visits were below the LLOQ (BLQ) in both the treatment arms. At those time points, mean values for plasma concentrations were similar in both treatment arms, supporting biosimilarity.

The maximum concentration of systemic aflibercept was higher in the Eylea arm (244.30 ng/ml) compared to MYL-1701P (108.40 ng/ml) at V2 (Tmax). However, as maximum concentrations at V7A (Cmax at steady state) as well as mean concentrations at Tmax and Cmax at steady state were comparable between groups, no concern regarding biosimilarity is expected from this observation. Reassuringly, there was no sign of accumulation of free aflibercept after repeated intravitreal dosing.

No considerable differences in plasma levels were observed between ADA positive and ADA negative subjects. However, the number of ADA positive subjects in the PK subset was too small for meaningful interpretation of these data.

In conclusion, the overall complementary PK assessment in a subset of DME patients supports biosimilarity between MYL-1701P and Eylea.

Pharmacodynamics: No dedicated comparative PD investigations have been performed as part of the clinical biosimilarity exercise. This is accepted, as there are no applicable laboratory PD markers that could serve as specific surrogates for clinical efficacy and safety of aflibercept. PD aspects were sufficiently addressed by including CRT over time as secondary endpoint in the pivotal clinical study MYL-1701P-3001.

2.4.3. Conclusions on clinical pharmacology

Assessment of systemic aflibercept levels conducted in a subset of patients in the pivotal clinical study MYL-1701P-3001 support biosimilarity, as mean aflibercept plasma concentrations at Cmax were similar between the reference product Eylea and biosimilar Yesafili.

The use of a non-EU reference product in this clinical trial is accepted.

2.4.4. Clinical efficacy

2.4.4.1. Main study

MYL-1701P-3001

This was a multi center, randomized, double masked, active controlled, comparative clinical study to demonstrate that no clinically meaningful differences exist between MYL-1701P and US-licensed Eylea in subjects with Diabetic Macular Edema (DME).

The maximum planned study duration from screening to end of the study was up to 13 months/56 weeks.

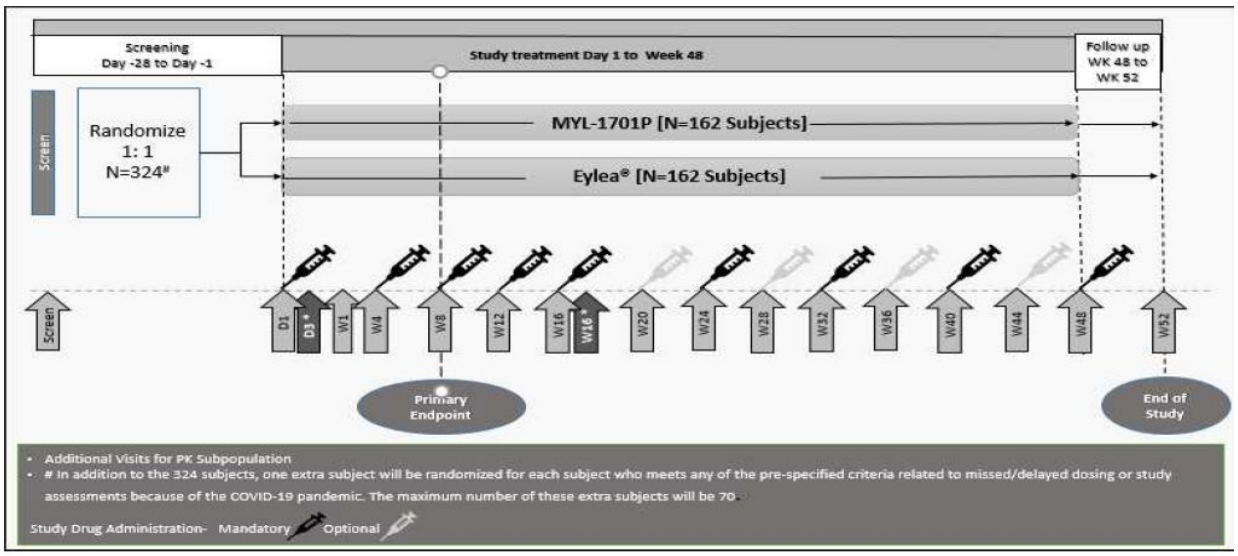


Figure 2. Study Design

Methods

Study Participants

Inclusion criteria (shortened)

1. Male or female subjects age ≥ 18 years.
2. Subjects with type 1 or type 2 diabetes mellitus who present with central DME involvement (defined as retinal thickening with a measurement of ≥300 µm involving the 1 mm CRT by SD-OCT) in the study eye.
3. The cause of decreased vision in the study eye was attributed primarily to DME by the Investigator.
4. Subjects who had BCVA at 4 m from 73 to 38 letters (ETDRS chart) equivalent to Snellen visual acuity of 20/40 to 20/200 in the study eye.
5. Subject was able to understand and voluntarily provide written informed consent to participate in the study.
6. If female of child-bearing potential, the subject must have been found negative for serum pregnancy test at the Screening visit and found negative for urine pregnancy test at baseline visit and was not nursing or planning a pregnancy.
7. If female of child-bearing potential, subject had to practice an acceptable form of birth control (regional differences).
8. If male, subject had to be surgically or biologically sterile. If not sterile, the subject had to agree to use an acceptable form of birth control with sexual partner or to abstain from sexual relations during the study period and up to 90 days following the last treatment dose.
9. Subject was willing to comply with the study duration, study visits and study related procedures.

Exclusion criteria

1. Subjects with known hypersensitivity to aflibercept or any of the excipients in MYL-1701P and Eylea
2. Known hypersensitivity to fluorescein
3. Ocular media of insufficient quality to obtain fundus and OCT images
4. Subjects were excluded if any of the following conditions were met in the study eye:
    a) Subjects with a history of vitreoretinal surgery in study eye and/or including scleral buckling
    b) Subjects who have had panretinal or macular laser photocoagulation within 3 months of randomization
    c) Subjects with history of use of intraocular corticosteroids anytime in the past or periocular (subconjunctival, intra-scleral, sub-tenon or retrobulbar) corticosteroids within 4 months of randomization

d) Subjects who had reduced vision due to causes other than DME, with the exception of requirement for spherical correction, or mild cataract assessed by the Investigator as not interfering with assessment of BCVA or CRT

e) Subjects with active proliferative diabetic retinopathy (PDR)

f) Subjects with active ocular inflammation

g) Subjects who have had cataract or other intraocular surgery within 3 months of randomization or expected to undergo cataract surgery or capsulotomy during the study duration

h) Subjects who have had laser capsulotomy within 3 months of randomization

i) Subjects with aphakia, whether congenital or surgical

j) Subjects with vitreous haemorrhage

k) Subjects with visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT that is thought to affect central vision

l) Subjects with myopia of spherical equivalent of ≥ 8 diopters, prior to any possible refractive or cataract surgery

m) Subjects with any other disease that might have compromised visual acuity or required medical or surgical intervention during the study period, or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole or choroidal neovascularization of any cause)

n) Structural damage to the center of the macula that was likely to preclude improvement BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates based on the Investigator's discretion with help of FA/FP and OCT.

o) Subjects with uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication); subjects with controlled glaucoma may participate in the study. [For India - Subjects with a clinical diagnosis of glaucoma (controlled or uncontrolled)].

p) Surgery for glaucoma in the past or likely to be needed in the future

q) Intraocular pressure ≥25 mm of Hg in the study eye

r) Prior treatment with verteporfin (photodynamic therapy)

5. Subjects were excluded if any of the following conditions were met in either eye:

   a) Subjects with active iris neovascularization

   b) Subjects with preretinal fibrosis involving the macula

   c) Subjects with history of idiopathic or autoimmune uveitis

   d) Subjects with active or suspected ocular or peri-ocular infection including but not limited to infectious blepharitis, keratitis, scleritis, or conjunctivitis

6. Subjects who received previous therapy with antiangiogenic drugs for either eye (pegaptanib, bevacizumab, ranibizumab, aflibercept).

7. Subjects who have received previous systemic antiangiogenic drugs (bevacizumab, aflibercept).
8. Subjects with current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol.
9. Subjects who had planned to participate in another clinical study while enrolled in this study and/or who had received an investigational drug and/or device within 30 days or 5 half-lives, whichever is longer, prior to screening.
10. Subject who was receiving treatment for a serious systemic infection.
11. Subjects with uncontrolled diabetes mellitus as defined by glycosylated hemoglobin (HbA1c) ≥ 10% at screening
12. Subjects with uncontrolled hypertension defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg.
13. Subjects with a history of cerebrovascular accident or myocardial infarction within 6 months of randomization.
14. Subjects with renal failure requiring dialysis or renal transplant.
15. Subjects who had only one functional eye, even if the eye met all other study requirements, or who had an ocular condition on the fellow eye with a poorer prognosis than the study eye.
16. Presence or history of malignant neoplasm (including lymphoproliferative disease), except for adequately treated basal cell carcinoma and cervical carcinoma in situ; or any malignancy with complete remission of more than 5 years.
17. Subjects with a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, psychiatric disease, or any other condition, that in the opinion of the Investigator would jeopardize the safety of the subject or the validity of the study results.

Sentinel Dosing Cohort

Since this was the first in human study of MYL-1701P, a sentinel cohort dosing was planned. Safety was to be first evaluated in a sentinel cohort of 9 subjects, with at least 3 subjects receiving MYL-1701P. Upon enrolment of the 9th subject in the sentinel cohort, enrolment had to be stopped. Enrollment could be reinstated based on the final decision of the Sentinel Cohort Data Review Committee (SCDRC). Only if the SCDRC confirmed that there are no safety concerns, the remainder of the study subjects could be enrolled into the study and dosed per protocol.

Inclusion and exclusion criteria are largely in line with registrational studies for Eylea and Scientific Advice and therefore deemed acceptable. Although a baseline BCVA range of 50-69 letters would have been preferred by EMA, the selected range (38-73 letters) may be suitable, with the caveats that assessment of decreases in visual acuity may be difficult in legally blind patients, i.e. 38 letters of BCVA (20/200), and there may be limited room for improvement in subjects with a BCVA of 73 letters (20/40). Upon request, the Applicant provided separate subgroup analyses for the preferred range of 50-69 letters to ensure an overall view of the treatment effect in the most sensitive part of the subjects.

Treatments

The use of US-sourced Eylea as reference product is acceptable.

Subjects received intravitreal injections of either 2 mg MYL-1701P or 2 mg US-Eylea throughout the 52-week treatment period, with planned doses at Study Day 1, Day 29 (week 4), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), Day 169 (Week 24), Day 225 (Week 32), Day 281 (Week 40) and Day 337 (Week 48).

In addition to the nine planned doses, study drug administration was also allowed at Week 20, Week 28, Week 36 and Week 44 based on the visual acuity, and/or SD-OCT at that visit and in accordance with the "criteria for administering additional 4-weekly doses" (see below; following the q4w dosing for the first 5 injections) or at the Investigator's discretion.

The additional doses were administered by the investigator only if the subject met any of the following criteria:

- Worsening of visual acuity, demonstrated as decrease in ETDRS by $\geq$ 5 letters from previous scheduled visit
- Increase in CRT by $\geq 50\,\mu$m as measured by SD-OCT, from previous scheduled visit

In the rare case, if the Investigator intended to administer additional dose for any reason, other than the criteria described above, the same was to be discussed and approved by the study medical monitor and the same was adequately documented.

Criteria for IP Discontinuation

Treatment was to be discontinued if any of the following reasons applied (but were not limited to):

- The subject withdrew the consent.
- Pregnancy.
- At the investigator's discretion, if it was in the subject's best interest due to occurrence of an AE and/or other findings considered to present a safety concern to continued dosing with study drug, which included but not limited to:
    - Development of hypersensitivity reaction suspected to be attributable to study drug which may have contraindicated the continued dosing with the study drug
    - Development of ocular or periocular infection, active intraocular inflammation which may have contraindicated the continued dosing with the study drug
- Despite education/reinforcement, the subject showed persistent inadequate compliance with required study visits/procedures, potentially compromising safety monitoring while on study drug based on investigator's discretion.
- Use of prohibited therapy presenting a safety concern to continued dosing with study drug
- At the investigator's discretion, in certain situations such as disease flare, progression, or nonresponse that required treatment with a prohibited medication or procedure, which in the opinion of the investigator warranted treatment withdrawal.
- If the mask (blinding) was broken for a subject by the Investigator

For discontinued subjects, documented follow-up by phone or in person was performed. Subjects who prematurely terminate study will have an Early Termination (ET) visit scheduled as soon as possible.

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have been withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF.

Subjects discontinued from the study were not replaced.

Objectives

Primary Objective

To evaluate the clinical equivalence of Yesafili and Eylea over 8 weeks of treatment at doses and regimen recommended by the Prescribing Information for Eylea, as assessed by change from baseline to Week 8 in BCVA.

Secondary Objectives

The key secondary objective of this study was:

- To compare the efficacy of Yesafili and Eylea as measured by change in central retinal thickness (CRT) over time

The other secondary objectives were:

- To compare the efficacy of Yesafili and Eylea as measured by change in BCVA over time
- To compare safety, tolerability, pharmacokinetics, and immunogenicity over time of Yesafili and Eylea
- To compare the number of study drug injections administered over the treatment period
- To compare impact of immunogenicity on efficacy and safety

The safety profile and immunogenicity are discussed in section 2.4.7. and Clinical PK is discussed in section 2.4.1.1.

Outcomes/endpoints

Primary Endpoint

The primary efficacy endpoint was the mean change from baseline in BCVA as assessed by ETDRS letters at Week 8.

Secondary Endpoints

The key secondary efficacy endpoint was

- The mean change from baseline in CRT as determined by spectral-domain-optical coherence tomography (SD-OCT) over time

The other secondary efficacy endpoints were:

- The mean change in BCVA over time

- Proportion of subjects who gained ≥15 letters from Baseline in BCVA, assessed in change from baseline in ETDRS letters over time
- Number of administrations of study drug required

Sample size

With equivalence limits of (-3, +3) letters, together with an assumed true treatment difference of zero letters, a standard deviation (SD) of 7.06 letters, and with 95% two-sided CIs, 145 evaluable subjects per arm provide 90% power. A total of 324 subjects were planned to be randomized at a 1:1 ratio to each arm after allowing for approximately 10% dropouts.

The study was conducted during COVID-19 pandemic and the impact of COVID-19 on the study is provided in detail in Section 9.8.4 of MYL-1701P-3001, 52-Week CSR. In addition, as per Protocol Version 3.0 (dated 09 Jun 2020), one extra subject was to be randomized for each subject who met any of the three following pre-specified criteria because of the COVID-19 pandemic:

Missed study drug administration at Visit 4 / Week 4

Missed BCVA examination for the study eye at Visit 5 / Week 8

Delayed BCVA examination for the study eye at Visit 5 / Week 8 by more than 7 days from the scheduled visit date

Given the dynamic nature of the pandemic and recruitment to the date of Protocol Version 3.0 (09 Jun 2020), the maximum number of these extra subjects was determined to be 70. The number of extra subjects required were determined by the review of protocol deviations related to the above-mentioned criteria. The review was done at the time of restarting recruitment after a brief hold in recruitment because of COVID-19 pandemic.

Randomisation and blinding (masking)

Blinding (masking)

Considering the ophthalmology indication, the term "masking" has been used instead of "blinding" throughout the protocol.

A 24-week CSR was developed after the last subject completed the 24 weeks of study participation. This final clinical study report (52-week CSR) was developed after the last subject completed 52 weeks of study participation. This CSR contains the efficacy, safety, pharmacokinetics, and immunogenicity data through 52 weeks for all randomized subjects.

At the time of 24 Week CSR, a pre-identified team was unmasked, and rest of the study team continued to be masked until the database lock for the Week 52 analysis. Unmasking of treatment code for final data analysis had to be done after database lock.

The investigators and subjects were masked to individual participant treatment assignment for as long as the individual participant remained in the study. Upon request, the Applicant clarified that investigators and participants continued to be masked even after individual participants completed the study and that the general unmasking was performed after the database lock. Further, the unmasking procedure for investigators, patients, sponsors and other staff was explained and it was concluded that unmasking did not influence study integrity.

Masked Personnel: Investigator was masked throughout the study. Investigator/designee performed all study assessments prior to and following study drug administration. Investigator had also to decide on the requirement of optional injections as necessary.

Unmasked Personnel

If an alternate ophthalmologist was available at the site:

An alternate ophthalmologist was identified to be responsible for preparation and administration of the study drug. Ophthalmologist administering the study drug performed the post injection procedures like measurement of IOP and any safety assessments up to 30 minutes after the study drug administration. However, the ophthalmologist administering the study drug did not perform any other study assessments including safety and efficacy assessments. If the unmasked ophthalmologist was not available at 30 minutes after dosing, the masked ophthalmologist performed post-dose safety assessments.

Additional unmasked site personnel were identified to be responsible for the receipt, tracking, preparation and destruction of study drug.

If an alternate ophthalmologist was not available at the site; and a qualified unmasked Pharmacist or Physician Assistant was available at site:

In cases, where the site did not have an alternate ophthalmologist, a qualified unmasked study personnel, i.e., unmasked pharmacist, physician assistant, was identified to be responsible for the receipt, tracking, preparation and destruction of study drug. The identified qualified pharmacist/physician assistant prepared the drug and handed over the syringe to the masked Investigator for intravitreal administration.

There was a possibility that unmasked person may come to know of treatment assignment while preparing the study drug for administration due to minor differences in the look and feel of the vials. MYL-1701P vial had a light grey stopper cap while the Eylea vial had blue stopper cap. This is acceptable, as responsibilities of unmasked personnel included preparation of study drug, but study drug administration was performed by the masked Investigator [except when alternate (unmasked) ophthalmologist was identified at site, see above].

The central SD-OCT assessment, and central laboratory assessment, including safety, PK and immunogenicity, were performed by the masked personnel.

The responsibilities of the **masked personnel** are as follows:

- Perform all screening procedures up until randomization
- Assess inclusion/exclusion criteria
- Obtain medical, surgical, ophthalmic, and smoking history
- Obtain informed consent
- Collect and process samples for laboratory testing
- Acquire SD - OCT, fundus photography (FP), and fluorescein angiography (FA) images and transfer them to reading centers
- Acquire ECGs
- Perform study drug administration (when preparation of study drug is done by an identified unmasked pharmacist, physician assistant at the site)

- Perform post-treatment safety assessments (except for post injection procedures like measurement of IOP and any safety assessments up to 30 minutes after the study drug administration when there was an identified unmasked ophthalmologist).
- Decide on need for additional treatment, if any
- Assess AEs, including severity and relationship
- Perform complete OE at all study visits
- Evaluate all safety, including review of images for safety concerns at the site
- Evaluate vital signs and ECGs; perform physical examinations
- Test refraction and BCVA
- Check IOP
- Assess SD - OCT, FP/FA.

Responsibilities of the **Unmasked Personnel** are as follows:

- Receipt, tracking, and destruction of study drug
- Prepare study drug
- Study drug administration and post injection procedures like measurement of IOP and any safety assessments up to 30 minutes after the study drug administration (when alternate ophthalmologist is identified at the site)

Breaking the Mask

The masked treatment code was not to be broken, except in emergency situations for which the identification of the study treatment of a subject was required by the Investigator in case of a medical emergency and when the knowledge of the study treatment allocation was required for appropriate management of the medical event.

Unmasking of treatment code for final data analysis had to be done after database lock. Unmasking process had to be performed in accordance with both Sponsor's and CRO's unmasking SOPs, as detailed in the statistical analysis plan (SAP).

In an event if the mask was broken for a subject by the Investigator, that subject had to be withdrawn from the study. Upon request, the Applicant confirmed that no patient was withdrawn following breaking the mask. Furthermore, according to the protocol, if an alternate ophthalmologist was available at the site, unmasked personnel was responsible for preparation and administration of the study drug. According to the Applicant, unmasked personnel did not have true unmasked information. Reassuringly, to avoid the risk of unmasking at the site level, two separate teams were formed: the masked team was responsible to review efficacy and safety endpoints, whereas the unmasked team was responsible to handle study drug management (receipt, administration and destruction). Hence, the unmasked investigator administering the study drug did not participate in any efficacy or safety endpoint evaluations apart from the immediate post-injection period (30 minutes post-injection). It is therefore agreed that no impact on study integrity is expected.

Statistical methods

Efficacy

The primary efficacy endpoint was the mean change from baseline in BCVA as assessed by ETDRS letters at Week 8.

The primary analysis of the primary endpoint was based on an MMRM analysis on mean change from baseline in BCVA as assessed by ETDRS letter score at, Week 8. This analysis was based on data collected up to Week 8.

This model will include treatment, visit/time (in weeks), treatment-by-visit interaction, and region as fixed effects and baseline BCVA as a covariate. The within subject variance-covariance matrix was assumed to be unstructured (which does not presume a particular correlation structure for repeated measurement within subjects over time), estimation used restricted maximum likelihood, and the denominator degrees of freedom used the Kenward-Roger estimate. The MMRM model results are presented with an estimate (Least Square [LS] means), standard error, and 95% two-sided CIs for the treatment difference (with Eylea group being the reference category) at week 8.

Per EMA's requirement, equivalence was demonstrated if the treatment difference of mean change in BCVA, from baseline to Week 8 based on 95% CI was fully contained within the interval (-3, 3). The primary efficacy analysis was performed on the ITT analysis set and it included data from all visits regardless of whether the subject was still receiving study medication.

The following sensitivity analyses of the primary endpoint were performed:

- Full Analysis Set (FAS).
- Per protocol (PP) Analysis Set.
- Where BCVA values after discontinuing study medication were excluded.
- Where missing BCVA values at Week 8 were replaced by LOCF approach using the analysis of covariance (ANCOVA) model.
- Tipping point analysis for delta method using multiple imputation.

Additional sensitivity and supplementary analyses were conducted to assess the impact of COVID-19-related disruptions on the study.

It is critically noted, that no reference to the E9(R1) terminology in regard to estimands are made in the CSR. For transparency purposes, it would be preferred to include results of analyses that use the appropriate estimations for targets of estimation that are relevant to this type if study objective. That is, both estimands employing "hypothetical" for all intercurrent events and "treatment policy" for all intercurrent events. Of note, for the most relevant intercurrent events these analyses were in essence already conducted (but reported as sensitivity analyses). Hence, the comment is minor and for transparency purposes only.

Subgroup analyses were performed for the primary efficacy endpoint based on the parameters baseline BCVA, age, gender, race, ethnicity, geographic region, baseline HbA1c, use of anti-VEGF therapy in fellow eye prior to week 8 and ADA status.

The key secondary efficacy variable was the mean change from baseline in CRT as determined by SD-OCT at Week 8 (corresponding tables were prepared for the 24-week analysis only).

The analysis of the key secondary efficacy variable was performed in a similar manner as the analysis of the primary efficacy endpoint using central CRT reading of all the SD-OCT images across visits including subgroup analyses and forest plot for subgroups.

The mean change in BCVA over time was analyzed in a similar manner as the primary efficacy endpoint, but the analysis was to be based on data collected up to the data cut for the respective

clinical study report (CSR; Week 24 or Week 52). The proportion of subjects who gained ≥15 letters from baseline in BCVA across visits were presented by treatment. The same summary was also presented for subjects who gained ≥5 and ≥10 letters as well as subjects who lost ≥5, ≥10 and ≥15 letters.

The number of intravitreal injections of study drug administered over the treatment period was descriptively summarized.

Pharmacokinetics

Pharmacokinetics (free aflibercept concentrations) was evaluated for subjects participating in pharmacokinetic (PK) subset. At least 32 subjects in each study arm were planned to be included in the PK subset. Overall, 89 subjects consented and participated in the PK subset (42 subjects in the MYL-1701P arm and 47 subjects in the Eylea arm).

The PK subset analysis set consisted of all subjects who consented for participation in PK subpopulation and have at least one measured concentration of study drug. The patients enrolled under this PK sub-study had a separate stratification at the IWRS level to ensure equal distribution among the treatment groups. The PK sampling was to be done in these subjects as per the Study Schedule. This strategy is acknowledged.

All concentrations below the lower limit of quantification (LLOQ, i.e. below 15.0 ng/mL) values have been analyzed as '0'. While in principle this is not a conservative imputation, the concentrations are considered overall very low, so that an imputation with the LLOQ would not change the overall conclusion that concentrations are low in both treatment arms, and therefore no concern arises. In the summary tables, a row indicates the number of subjects with aflibercept concentrations below LLOQ.

Analyses Sets

All deviations/violations and exclusions of subjects from analysis sets were identified and finalized at the blinded data review (BDR) meeting prior to the study unmasking for the 24-week analysis.

The **intention-to-treat (ITT) analysis set** consisted of all subjects who were randomized. Subjects were included in the analysis according to the treatment to which they were randomized. The ITT analysis set was the primary analysis set for efficacy analyses.

The **safety analysis set (Safety Set)** consisted of all subjects who received at least one dose of study drug. Subjects were included in the analysis according to the actual treatment received. The safety analysis set was the primary analysis set for safety analyses.

The **full analysis set (FAS)** consisted of all randomized subjects who received any study drug, who had a baseline BCVA, and who also had at least one post dosing BCVA assessment up to Week 8.

Subjects were included in the analysis according to the treatment to which they were randomized. The FAS provided supportive data for the primary efficacy analysis.

The **per-protocol (PP) analysis set** consisted of all FAS subjects who had no major protocol deviations (i.e., no violation which affected the primary efficacy outcome). Major protocol deviations included one or more of the following categories:

- Did not receive treatment to which they were randomized
- Inclusion/exclusion criteria violations which can impact the primary efficacy analysis
- Intake of forbidden concomitant medication which can impact the primary efficacy analysis
- Treatment deviation (missed 1 or more injections prior to Week 8)

In addition, further deviations were considered major if they impacted the primary efficacy analysis. Potential protocol deviations were collected during the study within ICON's ICOTRIAL system. The list of subjects excluded from the PP analysis set and the precise reasons for exclusion were finalized at the BDR meeting held prior to database lock for Week 24 (Section 2.1.3 of BDR report V1.0).

The **PK subset analysis** set consisted of all subjects who had signed the ICF for participation in PK subpopulation and had at least one measured concentration of study treatment.

The **SAP** (Version 1.0) was finalized on 08 Jan 2019 and amended on 29 Jan 2021 (Version 2.0) and on 21 Apr 2021 (Version 3.0).

Changes to the planned analysis is detailed in SAP Version 3.0: For mean change from baseline in CRT over time, the following two additional analyses were performed: (1) using the investigator assessment and (2) central reading including indeterminate values.

(1) According to final SAP version 3.0, for the analysis of the secondary endpoint mean change from baseline in CRT, only the central reading was considered and, the CRT values provided by the Investigators based on their evaluation of the SD-OCT scan images were not considered. An additional analysis was performed utilizing the CRT values recorded by the Investigators. In addition, a line graph with time (in weeks) presented on the x-axis and mean change from baseline in CRT presented on the y-axis was provided with LOCF imputation method for the ITT analysis set.

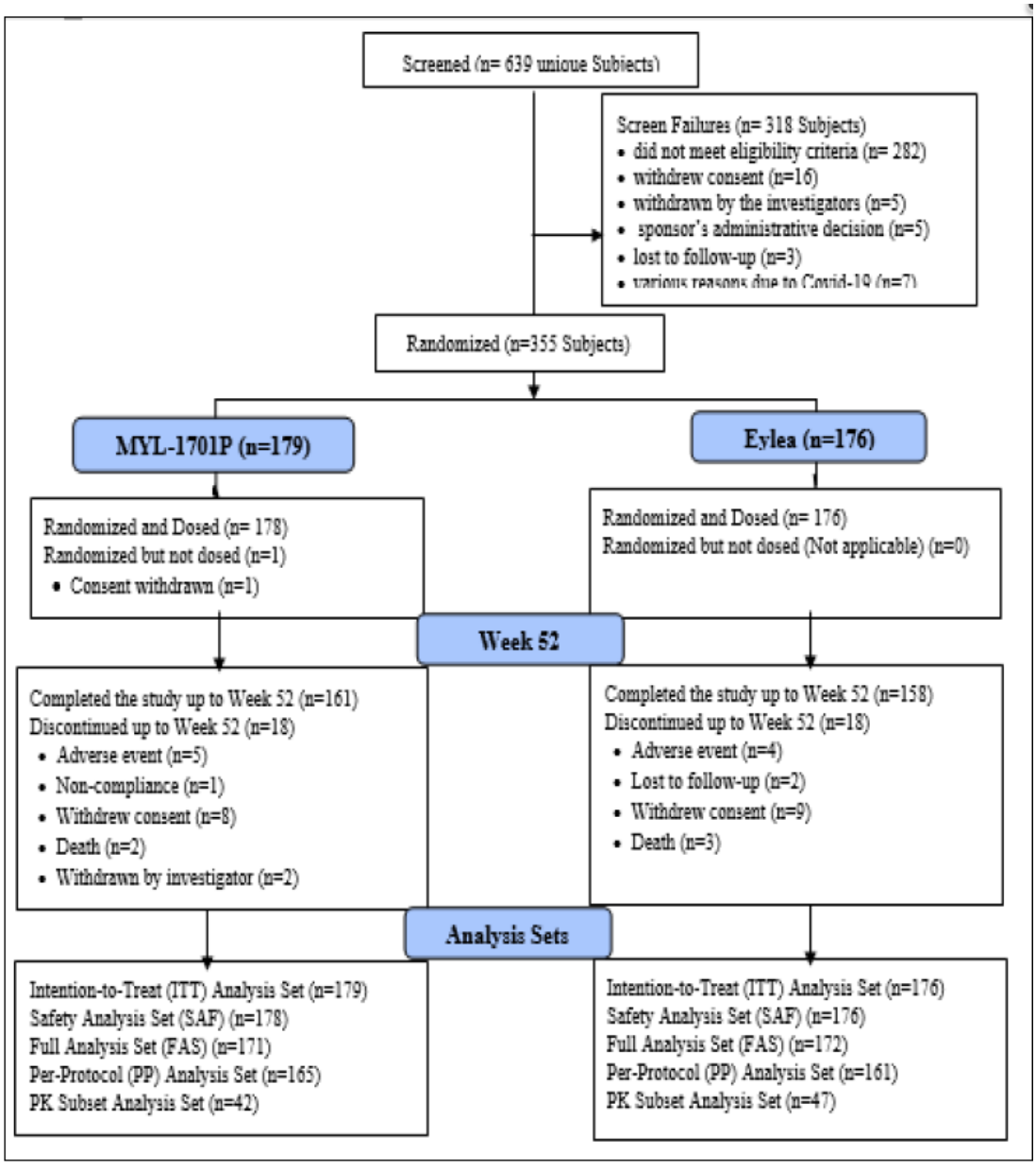
(2) The secondary analysis in SAP utilizing the central reader CRT values did not consider the values that were flagged as 'indeterminate'. According to the standard operating procedures of the central reading center, the reader would have indicated a CRT value as "indeterminate" in cases where the SD-OCT images had some quality issues such as poor segmentation or centering. An additional analysis was performed using all CRT values including any values flagged as indeterminate. In addition, a line graph with time (in weeks) presented on the x-axis and mean change from baseline in CRT presented on the y-axis was provided with LOCF imputation method for the ITT analysis set.

Handling of missing data and outliers

Missing data will not be imputed in the primary analysis of the primary efficacy endpoint. No imputation will be employed for the descriptive summaries and listings. Missing post-baseline values will be imputed using the last observation carried forward (LOCF) before calculating the proportions of subjects who gained or lost letters (secondary efficacy endpoints). The LOCF imputation used for the above sensitivity analyses is not considered conservative for the hypothesis of equivalence testing and does therefore not provide strong additional support in favour of equivalence.

Results

Participant flow



Abbreviations: n = number of subjects in the specified category with non-missing values.
Source: Table 14.1.1.1b, Table 14.1.1.2b; Listing 16.2.1.1b and Listing 16.2.1.2b.

Figure 3. Subject Disposition Chart

As per protocol V 3.0, one extra subject was to be randomized for each subject who met any of the pre-specified criteria related to missed/delayed dosing and/or study assessments because of the coronavirus disease 2019 (COVID-19) pandemic. In total, 31 additional subjects were randomized based on these criteria. Upon request, the Applicant clarified that no subjects were discontinued after meeting the pre-defined criteria to trigger randomization of an extra subject. The effort to increase the sample size is acknowledged.

A total of 639 (unique) subjects were screened; upon request, it was clarified that 34 re-screening events occurred, resulting in a total number of 673 screening events, of which 318 were screening failures. Hence, a total of 355 subjects were randomized with 179 subjects to the MYL-1701P arm and 176 subjects to the Eylea arm.

A total of 172 (96.1%) subjects in the MYL-1701P arm and 173 (98.3%) in the Eylea arm completed the study up to Week 8, and a total of 161 (89.9%) subjects in the MYL-1701P arm and 158 (89.8%) subjects in the Eylea arm completed Week 52 / End of Study Visit.

The treatment arms were similar in terms of proportion of subjects completing the study (161 [89.9%] in MYL-1701P arm vs 158 [89.8%] in Eylea arm). The observed high and similar retention rate in both treatment arms can be considered as supporting evidence that trial conduct was good with little need for data imputation and overall good interpretability of the obtained study data. The reasons for early discontinuation of subjects from the study were also comparable between the arms, withdrawal of consent (8 [4.5%] in MYL-1701P arm vs 9 [5.1%] in Eylea arm) being the most common reason followed by withdrawal due to adverse events (5 [2.8%] in MYL-1701P arm vs 4 [2.3%] in Eylea arm). Five deaths occurred: 2 (1.1%) in the MYL-1701P arm vs 3 (1.7%) in the Eylea arm.

Disposition of subjects per treatment arm in the ITT set is summarized in Table 3.

Table 3: Summary of Subject Status – All Subjects Randomized

Subject Disposition	MYL-1701P n (%)	Eylea n (%)	Overall n (%)
No. of subjects randomized	179	176	355
Randomized and dosed	178	176	354
Randomized but not dosed	1	0	1
No. of subjects completed the study up to Week 8	172 (96.1)	173 (98.3)	345 (97.2)
No. of subjects completed Week 52 study	161 (89.9)	158 (89.8)	319 (89.9)
No. of subjects discontinued study	18 (10.1)	18 (10.2)	36 (10.1)
Withdrew consent	8 (4.5)	9 (5.1)	17 (4.8)
Adverse event	5 (2.8)	4 (2.3)	9 (2.5)
Death	2 (1.1)	3 (1.7)	5 (1.4)
Withdrawn by investigator	2 (1.1)	0	2 (0.6)
Lost to follow-up	0	2 (1.1)	2 (0.6)
Non-compliance	1 (0.6)	0	1 (0.3)

N = number of subjects in the specified category with non-missing values. Note: Percentage (%) based on number of randomized subjects. Number of screened subjects includes multiple screening events, in total 639 unique subjects have been screened. Source: Table 14.1.1.1a, 14.1.1.1b; Listing 16.2.1.1a, 16.2.1.1b, 16.2.1.2a and 16.2.1.2b of MYL-1701P-3001, 52-Week CSR

Recruitment

Date first subject randomized: **23 Aug 2018**

Date last subject completed Week 52 / End of Study Visit: **10 Sep 2021**

Conduct of the study

Protocol Amendments

Protocol Version 1.0 dated 27 Nov 2017, was used for regulatory consultation with the USFDA and EMA. The suggestions from the Agencies were implemented in the Protocol Version 2.0 dated 07 Feb 2018. The study was initiated with Protocol Version 2.0 dated 07 Feb 2018. The Protocol Version 2.0 was updated to Protocol Version 3.0 dated 09 Jun 2020 to address the potential impact of COVID-19 pandemic. In addition, this amendment included minor modifications to inclusion and exclusion criteria, based on the feedback from Investigators and Country Agencies.

Protocol Deviations

Protocol deviations were categorized as key (or important) and non-key (or unimportant) based on protocol deviation criteria form (PDCF). The key and non-key PDs are summarized in Table 4.

The number of subjects with at least one key PD were comparable between the arms, 122 (68.2%) in MYL-1701P arm and 129 (73.3%) in Eylea arm.

Table 4: Summary of Key Protocol Deviations – ITT Set

Protocol Deviations	MYL-1701P (N=179) n (%)	Eylea (N=176) n (%)	Overall (N=355) n (%)
Total number of PD	862	1042	1904
No. of subjects reporting at least one PD	164 (91.6)	164 (93.2)	328 (92.4)
No. of key/important PD	360	424	784
No. of subjects reporting at least one key/important PD	122 (68.2)	129 (73.3)	251 (70.7)
Total No. of major PDs	7	14	21
No. of subjects reporting at least one major PD	5 (2.8)	11 (6.3)	16 (4.5)

N=number of subjects in the treatment group analysis set. PD= protocol deviation.
Source: Table 14.1.1.3b and Listing 16.2.2.1b

During the Blinded Data Review (BDR) for 24 Week analysis, a total of 21 key PDs in 16 subjects were classified as major (7 deviations in 5 (2.8%) subjects in the MYL-1701P arm and 14 deviations in 11 (6.3%) subjects in the Eylea arm) and those subjects were excluded from the PP analysis set as described in the BDR report.

Major PDs in both arms are provided in Table 5.

Table 5: Major Protocol Deviations by Treatment Arms

Category	MYL-1701P	Eylea
Week 8 BCVA outside 7 days window period	4	6
Week 4 dose outside the 7 days window period	3	4
Use of prohibited medication	-	2
Eligibility criteria not met	-	1
Week 8 BCVA performed after Week 8 dose	-	1

Source: Listing 16.2.2.1a

GCP Inspections

This study was subject to audit by the Sponsor or designee at intervals to ensure that the clinical study was conducted, and data were generated, documented (recorded), and reported in compliance with the study protocol; ICH, GCP E6 consolidated guidelines; and other applicable regulations.

Measurements of Treatment Compliance

The compliance to the study treatment, as measured by the proportion of planned injections received, was similar between both the treatment arms (93.0% in the MYL-1701P arm vs 94.4% in the Eylea arm; see Section *2.4.7.1. Patient exposure*, Table 3).

The median treatment duration was 364 days in each of the study arms. The mean (SD) number of doses received in each of the treatment arms was similar [8.4 (2.06) in MYL-1701P arm and 8.7 (1.76) in Eylea arm]. Majority of the subjects in both arms maintained an overall compliance of ≥75% for the planned doses. (89.3% in MYL-1701P arm and 94.9% in Eylea arm). There was a higher proportion of subjects in the MYL-1701P arm who missed more than 2 planned doses compared to Eylea arm (8.4% vs 4.0%) which is leading to a slightly lower proportion of subjects in MYL-1701P arm having

compliance of ≥75% compared to the Eylea arm. Majority of these missed doses were due to COVID-19 pandemic related missed study visits.

A total of 96 (27.1%) subjects received at least one additional dose of study drug treatment as per the criteria mentioned in Section *Treatments*. Out of these 96 subjects, 54 (30.3%) subjects in MYL-1701P arm and 42 (23.9%) subjects in Eylea arm received at least one additional optional dose of the study drug. This finding is in contrast to similar proportions of subjects receiving > 9 planned injections. The discrepancy can be explained by more additional optional doses in patients in the MYL-1701P arm, who received less than 9 planned doses, i.e. who missed planned doses (see *Other Secondary Efficacy Parameters*).

There were no dosing errors (like wrong study drug treatment received) reported in this study.

Baseline data

Demographics

The demographic profile of the subjects in the ITT population is summarized in Table 6.

In general, the demographic profile was balanced between treatment groups with respect to age, gender, race and ethnic origin.

Table 6: Summary of Demographic Data – ITT Analysis Set

Characteristic	MYL-1701P (N=179)	Eylea (N=176)	Overall (N=355)
Age (years)			
N	179	176	355
Mean (SD)	62.8 (8.37)	61.6 (9.93)	62.2 (9.18)
Min, Max	30, 80	27, 83	27, 83
Age group (years) n (%)			
< 55	32 (17.9)	38 (21.6)	70 (19.7)
≥55 - <65	69 (38.5)	68 (38.6)	137 (38.6)
≥65 - <75	65 (36.3)	56 (31.8)	121 (34.1)
≥75	13 (7.3)	14 (8.0)	27 (7.6)
Gender n (%)			
Male	107 (59.8)	109 (61.9)	216 (60.8)
Female	72 (40.2)	67 (38.1)	139 (39.2)
Geographical region/country n (%)			
US	32 (17.9)	31 (17.6)	63 (17.7)
Europe	87 (48.6)	87 (49.4)	174 (49.0)
Japan	22 (12.3)	19 (10.8)	41 (11.5)
Rest of the world (India)	38 (21.2)	39 (22.2)	77 (21.7)

Max=Maximum; Min=Minimum; SD=Standard deviation.
n=number of subjects in the specified category with non-missing values; N=number of subjects in the treatment group analysis set. Note: Missing data will be presented if at least one record is missing in the given category.
Source: Table 14.1.2.1.1a of MYL-1701P-3001,52-Week CSR

Baseline General and Disease Characteristics

At baseline, there were no notable differences between the treatment arms for body weight, BMI, HbA1c and smoking status of the subjects. The mean (SD) body weight was 81.80 kg (18.864). The mean (SD) BMI was 29.35 (5.859). The mean (SD) baseline HbA1c was 7.70% (1.074).

A tabular summary of the disease characteristics at baseline is provided in Table 7. Both treatment arms were well balanced with respect to ocular disease characteristics at baseline.

The majority (53.5%) of patients had high baseline BCVA of 65 or higher. As highlighted earlier, there may be limited room for improvement in patients with high BCVA and hence ceiling effects may affect assessment of biosimilarity. Subgroup analyses were conducted to assess possible confounding of the overall magnitude of treatment differences by a proportion of patients that is potentially less sensitive to identify treatment differences (discussed in Section *Ancillary analyses*).

The distribution of DRSS (diabetic retinopathy severity score) was similar across treatment arms. The ETDRS DRSS was 47 in 58% of the subjects denoting moderately severe non-proliferative diabetic retinopathy (NPDR). There was one subject with a DRSS score of 65 in the MYL-1701P arm, which denotes proliferative diabetic retinopathy (PDR). This subject was included in the study analyses as the PDR was not active with absence of any neovascularization, and therefore not meeting exclusion criterion 4e.

Table 7: Summary of Baseline Ophthalmologic Characteristics – ITT Set

Characteristic	MYL-1701P (N=179)	Eylea (N=176)	Overall (N=355)
	Study Eye	Study Eye	Study Eye
CRT (µ) CR [a]			
N	161	166	327
Mean (SD)	467.9 (116.44)	468.0 (124.07)	467.9 (120.19)
Min, Max	289, 774	278, 823	278, 823
Missing	18	10	28
CRT (µ)- IA [a]			
N	179	176	355
Mean (SD)	467.2 (120.72)	468.1 (122.84)	467.6 (121.60)
Min, Max	301, 927	301, 823	301, 927
Missing	0	0	0
BCVA (letters)			
N	179	176	355
Mean (SD)	62.7 (8.82)	63.9 (8.48)	63.3 (8.66)
Min, Max	38, 73	40, 73	38, 73
BCVA n (%)			
73-55	150 (83.8)	148 (84.1)	298 (83.9)
54-38	29 (16.2)	28 (15.9)	57 (16.1)
< 45	8 (4.5)	6 (3.4)	14 (3.9)
≥ 45 - < 55	21 (11.7)	22 (12.5)	43 (12.1)
≥ 55 - < 65	60 (33.5)	48 (27.3)	108 (30.4)
≥ 65	90 (50.3)	100 (56.8)	190 (53.5)
DR severity score n (%)			
10 [none]	1 (0.6)	0	1 (0.3)
20	1 (0.6)	5 (2.8)	6 (1.7)
35	12 (6.7)	7 (4.0)	19 (5.4)
43	21 (11.7)	22 (12.5)	43 (12.1)
47	101 (56.4)	105 (59.7)	206 (58.0)
53	42 (23.5)	37 (21.0)	79 (22.3)
61	0	0	0
65	1 (0.6)	0	1 (0.3)
71	0	0	0
75	0	0	0
90 [cannot grade]	0	0	0
IOP (mmHg)			
N	179	176	355
Mean (SD)	15.3 (2.87)	15.4 (2.97)	15.4 (2.92)
Min, Max	8, 24	8, 23	8, 24

CRT=Central retinal thickness; Max=Maximum; Min=Minimum; SD=Standard deviation, BCVA = Best-corrected visual acuity, IOP = Intraocular pressure; CR = Central Reading, IA = Investigator assessment, DR = Diabetic retinopathy. n=number of subjects in the specified category with non-missing values; µ=micron; N=number of subjects in the treatment group analysis set. [a] CRT was measured as central subfield thickness.
Note: Missing data will be presented if at least one record is missing in the given category.
Source: Table 14.1.2.3.1a

Medical and Surgical History

In general, both treatment arms were similar in terms of ocular and non-ocular medical and surgical history. All the subjects in either arm had at least one ocular and non-ocular medical history. All subjects had a history of diabetes mellitus (Type 1 or Type 2). The ocular and non-ocular medical and surgical history are typical of this study population.

Apart from the diabetic retinopathy and diabetic retinal edema, the most commonly reported ocular medical history in the study eye were cataract (MYL-1701P, 76 [42.5%] and Eylea, 63 [35.8%]), cataract nuclear (MYL-1701P, 15 [8.4%] and Eylea, 17 [9.7%]) and retinal haemorrhage (MYL-1701P, 9 [5.0%] and Eylea, 9 [5.1%]). The most common past ocular procedures reported for the study eye

included retinal laser coagulation (MYL-1701P, 27 [15.1%] and Eylea, 19 [10.8%]); cataract operation (MYL-1701P, 20 [11.2%] and Eylea, 24 [13.6%]); intraocular lens implant (MYL-1701P, 10 [5.6%] and Eylea, 9 [5.1]). A sufficient wash out period required by the study protocol had elapsed after the procedures at the time of randomization for all these subjects.

The most commonly reported non-ocular medical history were in the SOCs of Metabolism and nutrition disorders (MYL-1701P, 179 [100%] and Eylea 176 [100%]); Vascular disorders (MYL-1701P, 142 [79.3%] and Eylea 134 [76.1%]); Surgical and medical procedures (MYL-1701P, 64 [35.8%] and Eylea 62 [35.2%]); and Nervous system disorders (MYL-1701P, 47 [26.3%] and Eylea 58 [33.0%]).

Prior Medications and Treatments

Overall, 99.4% of the subjects had at least one prior medication (177 [98.9%] in MYL-1701P arm and 176 [100%] in Eylea). The proportion of subjects who were on specific classes of prior medications were largely similar across the two arms.

Apart from the mydriatics and the cycloplegics used during the screening procedures, the other most commonly used prior medications by anatomic therapeutic chemical class were blood glucose lowering agents (143 [79.9%] in the MYL-1701P arm and 144 [81.8%] in Eylea); insulins and its analogues (91 [50.8%] in the MYL-1701P arm and 90 [51.1%] in Eylea); and lipid modifying agents, plain (74 [41.3%] in the MYL-1701P arm and 79 [44.9%] in Eylea).

Concomitant Medications

Overall, 99.7% of the subjects received at least one non-study medication during the study (178 [99.4%] in MYL-1701P arm and 176 [100%] in Eylea arm).

It should be noted that the frequently reported topical anesthetics and antibiotics were part of pre-medications. Apart from these, the most frequently reported concomitant medications by PT were metformin (47 [26.3%] subjects in the MYL-1701P arm and 47 [26.7%] subjects in the Eylea arm), metformin hydrochloride (47 [26.3%] subjects in the MYL-1701P arm and 40 [22.7%] subjects in the Eylea arm), and tropicamide (78 [43.6%] subjects in the MYL-1701P arm and 96 [54.5%] subjects in the Eylea arm).

A significant proportion of subjects (100 [28.2%]) used intraocular anti-VEGF agents such as bevacizumab, ranibizumab and aflibercept in the fellow eye [45 (25.1%) subjects in the MYL-1701P and 55 (31.3%) subjects in the Eylea arm]. These medications were utilized as part of the standard of care management for the fellow eye disease. To investigate a possible confounding effect of concomitant anti-VEGF therapy in the fellow eye, subgroup analyses were conducted for the primary and key secondary endpoints [any anti-VEGF therapy in fellow eye prior to visit 5 (Week 8)(yes, no)].

In general, the demographic characteristics as well as other baseline parameters such as medical and ophthalmologic history, prior and concomitant medications were balanced between treatment arms.

Numbers analysed

Sample size targets for primary endpoint assessment (total n = 324) as well as PK subset (n = 32 per treatment group) have been met (Table 8).

Table 8: Analysis Populations – ITT Set

Analysis Population	MYL-1701P (N=179) n (%)	Eylea (N=176) n (%)	Overall (N=355) n (%)
Intention-to-Treat (ITT) Analysis Set [a]	179 (100)	176 (100)	355 (100)
Safety Analysis Set (Safety) [b]	178 (99.4)	176 (100)	354 (99.7)
Subjects excluded from Safety	1 (0.6)	0	1 (0.3)
Not treated	1 (0.6)	0	1 (0.3)
Full Analysis Set (FAS) [c]	171 (95.5)	172 (97.7)	343 (96.6)
Subjects excluded from FAS	8 (4.5)	4 (2.3)	12 (3.4)
Not treated	1 (0.6)	0	1 (0.3)
No BCVA score for study eye under study treatment up to Week 8	8 (4.5)	4 (2.3)	12 (3.4)
Per-Protocol (PP) Analysis Set [d]	165 (92.2)	161 (91.5)	326 (91.8)
Subjects excluded from PP population	14 (7.8)	15 (8.5)	29 (8.2)
Excluded from FAS	8 (4.5)	4 (2.3)	12 (3.4)
In FAS but missed at least 1 injection up to Week 8	1 (0.6)	0	1 (0.3)
Major PDs	5 (2.8)	11 (6.3)	16 (4.5)
PK Subset Analysis Set [e]	42 (23.5)	47 (26.7)	89 (25.1)
Subjects excluded from PK Subset Analysis Set	137 (76.5)	129 (73.3)	266 (74.9)
No informed consent for PK sub-population	136 (76.0)	129 (73.3)	265 (74.6)
Not treated	1 (0.6)	0	1 (0.3)

n=number of subjects in the specified category with non-missing values; N=number of subjects in the treatment group analysis set. Note: Percentage (%) based on number of randomized subjects. [a] The ITT Analysis Set consists of all subjects who were randomized. Subjects are included in the analysis according to the treatment to which they were randomized. [b] The Safety Analysis Set consists of all subjects who received at least one dose of study drug. Subjects are included in the analysis according to the actual treatment received. [c] The FAS consists of All Randomized Subjects who receive any study drug, who have a baseline BCVA, and who also have at least one post dosing BCVA assessment up to Week 8. Subjects are included in the analysis according to the treatment to which they were randomized. [d] The PP Analysis Set consists of all FAS subjects who have no major protocol deviations (i.e., no violation which may affect the study efficacy outcome). [e] The PK Subset Analysis Set consists of all subjects who have signed the ICF for participation in PK subpopulation and have at least one measured concentration of study treatment. Subjects are included in the analysis according to the actual treatment received.
Source: Table 14.1.1.2b; Listing 16.2.3a

Outcomes and estimation

The **primary efficacy endpoint** was the mean change from baseline in BCVA as assessed by ETDRS letter score, at Week 8. As defined by the Applicant, the primary analysis was performed on the **ITT analysis set** and included data from all visits up to Week 8 regardless of whether the subject was still receiving study medication (Table 9). The adjusted mean difference for mean change in BCVA from baseline to Week 8 was 0.04 letters and 95% CI was [-1.40, 1.47] which were within the pre-defined equivalence range of [-3, +3] letters. In both treatment groups, the effect size was what would be expected after treatment with aflibercept.

Table 9: Analysis of Mean Chane in BCVA from Baseline to Week 8 by MMRM – ITT Set

Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)
Visit 5 (Week 8) – Primary Endpoint		
Subjects with value at baseline and this week	163	165
Adjusted mean (SE)	6.60 (0.548)	6.56 (0.548)
90% CI	(5.69, 7.50)	(5.66, 7.46)
95% CI	(5.52, 7.68)	(5.48, 7.64)
Adjusted mean difference (SE)		0.04 (0.730)
90% CI		(-1.16, 1.24)
95% CI		(-1.40, 1.47)

As highlighted in EMA Scientific Advice, primary assessment of the ITT and PP analysis sets is equally important to demonstrate biosimilarity, and therefore considered co-primary in this assessment by the Rapporteur. The analysis of the primary efficacy endpoint in the **PP analysis set** is shown in Table 10. Also for this analysis the 95% CI was within the pre-defined equivalence range of [-3, +3] letters. Thus, biosimilarity was demonstrated based on the primary endpoint in the ITT and PP Analysis Sets.

Upon request, the Applicant clarified that numbers from the line item 'Subjects with value at baseline and this week [8]' present in most tables for primary and key secondary analyses do not refer to the number of patients included in the analyses (adjusted means, SEs, CIs). The Applicant confirmed that the MMRM was applied to the overall number of subjects stated in the respective analysis sets, which is acceptable. Yet, the assessment of the FAS showed identical outcomes to the ITT population, despite different numbers of subjects included. Since only few subjects are concerned (n = 8 for MYL-1701P; n = 4 for Eylea), identical results in both analysis sets may be based on the way these analyses were defined with respect to eligibility and availability of data.

Table 10: Analysis of Mean Change in BCVA from Baseline to Week 8 by MMRM – PP Set

Statistics [a]	MYL-1701P (N=165)	Eylea (N=161)
Visit 5 (Week 8) – PRIMARY ENDPOINT		
Subjects with value at baseline and this week	158	154
Adjusted mean (SE)	6.61 (0.556)	6.80 (0.565)
90% CI	(5.69, 7.53)	(5.87, 7.74)
95% CI	(5.52, 7.70)	(5.69, 7.91)
Adjusted mean difference (SE)		-0.19 (0.745)
90% CI		(-1.42, 1.04)
95% CI		(-1.66, 1.27)

The **key secondary efficacy endpoint** was mean change from baseline in CRT as determined by SD-OCT over time. There was a reduction in the CRT from Baseline to Week 8 in both the treatment arms (Table 11). In both groups, the magnitude of the change from baseline was what would be expected after treatment with aflibercept. The adjusted mean difference between treatment arms was 11.46 µm. While an equivalence range was not defined for CRT, the 95% CI [-6.22, 29.14] indicated that there does not seem to be a relevant difference between the treatment groups, as the estimated lower and upper limits were clearly below 50 µm, an increase in CRT, which is defined as clinically relevant to trigger additional dosing.

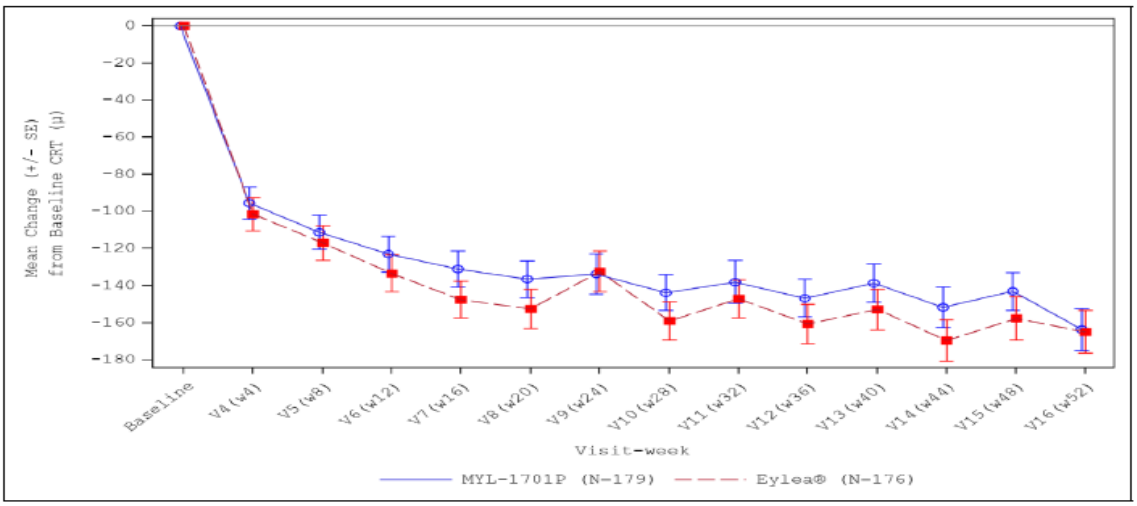
Table 11: Mean Change in CRT (µm) by MMRM from Baseline to Week 8 – ITT Set

Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)
Visit 5 (Week 8)		
Subjects with value at baseline and this week	135	137
Adjusted mean (SE)	-112.15 (6.742)	-123.61 (6.807)
90% CI	(-123.27, -101.02)	(-134.84, -112.38)
95% CI	(-125.41, -98.88)	(-137.00, -110.21)
Adjusted mean difference (SE)		11.46 (8.986)
90% CI		(-3.36, 26.29)
95% CI		(-6.22, 29.14)

The mean change from baseline for CRT over time is provided in Table 12 and Figure 4. Mean change in CRT throughout the entire study duration indicated an increase of improvement in both study arms. The adjusted mean difference between the study arms from Week 8 to Week 44 was consistently between 7-14 µm in favour of the Eylea arm, while a decrease of the adjusted mean difference between treatment arms from Week 48 was observed, with a minimal difference of 2.47 µm in favour of the MYL-1701P arm at Week 52. Overall, these differences are considered small, as those are very far below 50 µm, a change in CRT that would be considered clinically relevant. Hence, biosimilarity is supported by the key secondary efficacy endpoint CRT.

Table 12: Analysis of Mean Change from Baseline for CRT (µm) by MMRM – ITT Set

Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)			
			Adjusted mean difference	90% CI	95% CI
Visit 4 (Week 4) n	145	146			
Adjusted mean (SE)	-98.51 (7.022)	-101.97 (7.024)	3.46	(-12.09, 19.01)	(-15.08, 22.00)
Visit 5 (Week 8) n	135	137			
Adjusted mean (SE)	-112.77 (7.036)	-123.07 (7.023)	10.31	(-5.27, 25.89)	(-8.27, 28.88)
Visit 6 (Week 12) n	135	140			
Adjusted mean (SE)	-126.68 (7.031)	-137.18 (7.007)	10.51	(-5.05, 26.06)	(-8.04, 29.05)
Visit 7 (Week 16) n	132	137			
Adjusted mean (SE)	-134.68 (7.042)	-148.57 (7.017)	13.89	(-1.69, 29.47)	(-4.69, 32.46)
Visit 8 (Week 20) n	135	131			
Adjusted mean (SE)	-140.86 (7.027)	-152.00 (7.040)	11.14	(-4.45, 26.73)	(-7.44, 29.72)
Visit 9 (Week 24) n	126	129			
Adjusted mean (SE)	-130.68 (7.077)	-137.78 (7.064)	7.10	(-8.58, 22.77)	(-11.59, 25.78)
Visit 10 (Week 28) n	131	141			
Adjusted mean (SE)	-151.48 (7.057)	-161.87 (7.026)	10.39	(-5.21, 25.99)	(-8.21, 28.99)
Visit 11 (Week 32) n	117	135			
Adjusted mean (SE)	-138.63 (7.141)	-151.16 (7.067)	12.54	(-3.22, 28.29)	(-6.24, 31.31)
Visit 12 (Week 36) n	123	130			
Adjusted mean (SE)	-155.50 (7.119)	-167.09 (7.100)	11.59	(-4.18, 27.35)	(-7.20, 30.38)
Visit 13 (Week 40) n	123	128			
Adjusted mean (SE)	-145.12 (7.145)	-159.29 (7.128)	14.17	(-1.66, 30.00)	(-4.70, 33.05)
Visit 14 (Week 44) n	116	126			
Adjusted mean (SE)	-161.67 (7.193)	-169.22 (7.162)	7.55	(-8.38, 23.47)	(-11.43, 26.53)
Visit 15 (Week 48) n	120	126			
Adjusted mean (SE)	-156.12 (7.204)	-159.05 (7.188)	2.93	(-13.03, 18.89)	(-16.09, 21.96)
Visit 16 (Week 52) n	128	120			
Adjusted mean (SE)	-170.14 (7.198)	-167.67 (7.260)	-2.47	(-18.51, 13.56)	(-21.59, 16.64)
Visit 16 (EOT/EOS) n	133	123			
Adjusted mean (SE)	-168.24 (7.214)	-166.62 (7.284)	-1.62	(-17.70, 14.46)	(-20.79, 17.55)



Source: Figure 14.2.2.3.2b, Listing 16.2.6.2b of MYL-1701P-3001, 52-Week CSR

Figure 4. Line Plot for Mean Change in CRT (µm) from Baseline, Measured as Central Subfield Thickness (LOCF) ITT Analysis Set

Other Secondary Efficacy Parameters

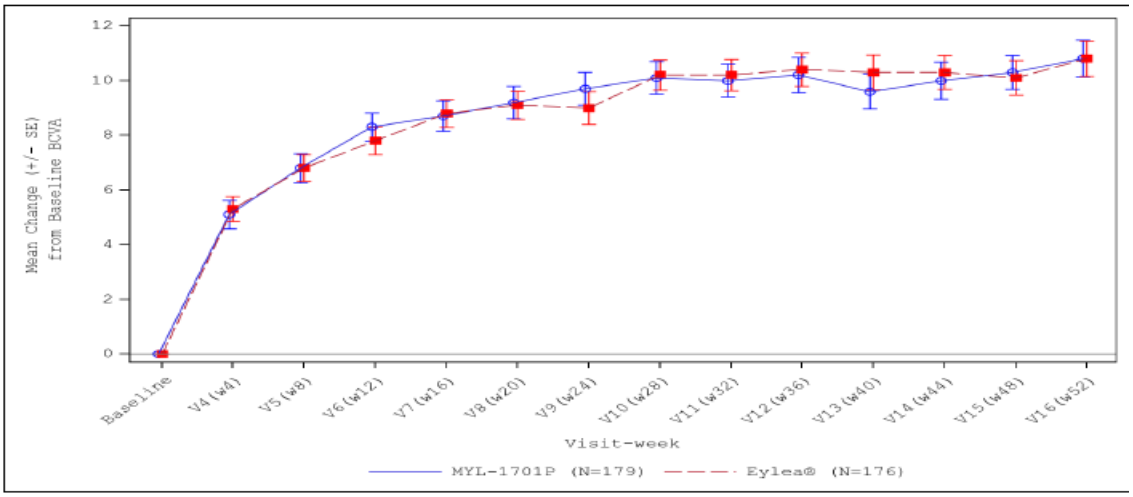
Other secondary endpoints included the mean change in BCVA over time up to Week 52 and the proportion of subjects who gained ≥15 letters at Week 52. Both analyses showed similar results between the two treatment groups, further supporting biosimilarity.

The analysis of **mean change in BCVA from baseline over time** has been provided in Table 13.

Table 13: Analysis of Mean Change from Baseline for BCVA by MMRM ITT - Set

Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)			
			Adjusted mean difference	90% CI	95% CI
Visit 4 (Week 4) n	171	172			
Adjusted mean (SE)	4.54 (0.608)	4.89 (0.611)	-0.35	(-1.70, 1.00)	(-1.96, 1.26)
Visit 5 (Week 8) n	163	165			
Adjusted mean (SE)	6.38 (0.611)	6.48 (0.613)	-0.10	(-1.45, 1.26)	(-1.71, 1.52)
Visit 6 (Week 12) n	161	160			
Adjusted mean (SE)	7.88 (0.611)	7.56 (0.615)	0.31	(-1.04, 1.67)	(-1.30, 1.93)
Visit 7 (Week 16) n	154	163			
Adjusted mean (SE)	8.17 (0.614)	8.48 (0.614)	-0.32	(-1.68, 1.04)	(-1.94, 1.30)
Visit 8 (Week 20) n	156	153			
Adjusted mean (SE)	8.66 (0.614)	8.79 (0.618)	-0.14	(-1.50, 1.23)	(-1.76, 1.49)
Visit 9 (Week 24) n	153	158			
Adjusted mean (SE)	9.33 (0.616)	8.61 (0.617)	0.72	(-0.64, 2.09)	(-0.90, 2.35)
Visit 10 (Week 28) n	150	161			
Adjusted mean (SE)	9.69 (0.618)	10.13 (0.616)	-0.44	(-1.80, 0.93)	(-2.07, 1.19)
Visit 11 (Week 32) n	149	160			
Adjusted mean (SE)	9.49 (0.619)	9.86 (0.617)	-0.37	(-1.74, 1.00)	(-2.00, 1.26)
Visit 12 (Week 36) n	154	159			
Adjusted mean (SE)	10.03 (0.618)	10.20 (0.618)	-0.17	(-1.54, 1.20)	(-1.80, 1.46)
Visit 13 (Week 40) n	151	159			
Adjusted mean (SE)	9.27 (0.620)	9.97 (0.618)	-0.70	(-2.07, 0.67)	(-2.33, 0.94)
Visit 14 (Week 44) n	146	157			
Adjusted mean (SE)	9.79 (0.622)	10.10 (0.619)	-0.31	(-1.69, 1.06)	(-1.95, 1.33)
Visit 15 (Week 48) n	155	156			
Adjusted mean (SE)	10.25 (0.620)	9.77 (0.620)	0.48	(-0.90, 1.85)	(-1.16, 2.11)
Visit 16 (Week 52) n	161	158			
Adjusted mean (SE)	10.76 (0.619)	10.52 (0.621)	0.24	(-1.13, 1.62)	(-1.40, 1.88)
Visit 16 (EOT/EOS) n	163	160			
Adjusted mean (SE)	10.75 (0.618)	10.54 (0.621)	0.21	(-1.16, 1.59)	(-1.42, 1.85)

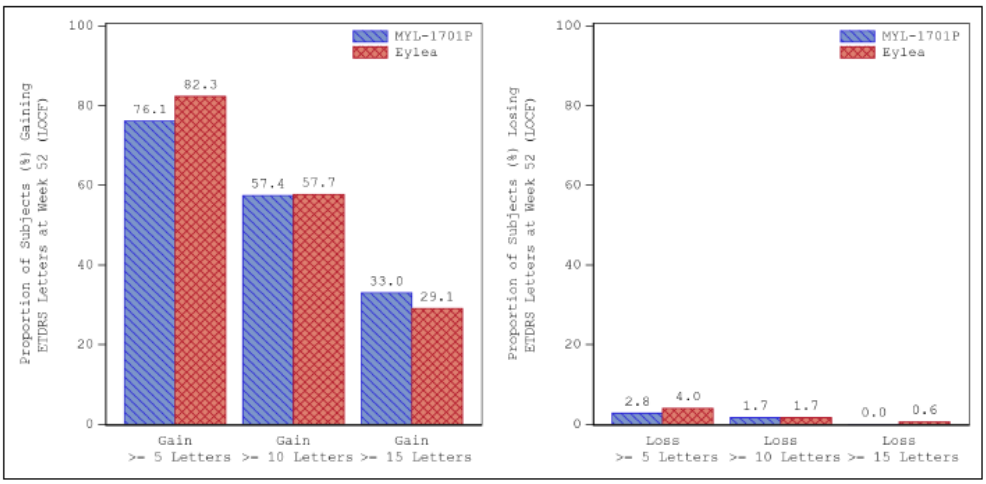
The time curve of mean change in BCVA over time up to Week 52 with LOCF imputation of the two treatment arms across visits is provided and Figure 5. The curves cross over time, with only marginal differences between the treatment arms at each visit.



Source: Figure 14.2.2.3.4b; Listing 16.2.6.5b of MYL-1701P-3001, 52-Week CSR

Figure 5. Line Plot for Mean Change in BCVA (LOCF) from Baseline – ITT Set

Figure 6 depicts the **proportion of subjects who gained** or lost ≥5, ≥10 and **≥15 letters** at Week 52 (LOCF). The proportion of subjects who gained or lost pre-specified number of letters at Week 52 was similar between the two treatment arms. Upon request, the Applicant performed an additional analysis on the secondary endpoint "proportion of subjects who gained or lost letters" with an alternative imputation technique that utilized a multiple imputation method, since LOCF imputation is not considered conservative for the hypothesis of equivalence testing. The results from this sensitivity analysis are consistent with the results from the pre-specified analysis, indicating robustness of the results.



Source: Figure 14.2.2.4.1b; Listing 16.2.6.5b Listing 16.2.6.5b of MYL-1701P-3001, 52-Weel CSR

Figure 6. Proportion of Subjects Who Gained or Lost ≥5, ≥10 or ≥15 Letters, at Week 52

The **number of injections of study drug administered** during the study period (ITT population) is provided in Table 14. The mean number of doses received during the 52 weeks of study were similar in both treatment arms [8.4 in MYL-1701P arm and 8.7 in Eylea arm]. The median number of doses received in each of the treatment arms was 9 injections (range: 1, 13).

Table 14: Summary of Administration of Study Drug Required Over Treatment Period – ITT Analysis Set

	MYL-1701P (N=179)	Eylea (N=176)	Overall (N=355)
Number of doses n (%)			
0	1 (0.6)	0	1 (0.3)
1	4 (2.2)	2 (1.1)	6 (1.7)
2	3 (1.7)	1 (0.6)	4 (1.1)
3	2 (1.1)	4 (2.3)	6 (1.7)
4	3 (1.7)	0	3 (0.8)
5	7 (3.9)	3 (1.7)	10 (2.8)
6	2 (1.1)	3 (1.7)	5 (1.4)
7	10 (5.6)	9 (5.1)	19 (5.4)
8	13 (7.3)	22 (12.5)	35 (9.9)
9	100 (55.9)	100 (56.8)	200 (56.3)
10	25 (14.0)	22 (12.5)	47 (13.2)
11	7 (3.9)	5 (2.8)	12 (3.4)
12	1 (0.6)	2 (1.1)	3 (0.8)
13	1 (0.6)	3 (1.7)	4 (1.1)

n=number of subjects in the specified category with non-missing values; N=number of subjects in the treatment group analysis set. Source: Table 14.2.7.1b, Listing 16.2.5b of MYL-1701P-3001, 52-Week CSR.

Per study protocol a total of nine injections were planned to be administered for the entire study duration of 52 weeks, with the option of receiving additional four doses upon worsening of BCVA or

CRT. Although the median number of doses received was indeed nine injections in both treatment arms, the median of discrete numbers is an insensitive metric, and indeed only 56.3% of all patients received nine doses. Reassuringly, upon request it was clarified that only few of those patients received additional doses due to worsening of their condition, since the majority of patients who received 9 doses have not received any additional dose (95%). As discussed above, more patients in the MYL-1701P arm received at least one additional dose of aflibercept (30.3%) compared to subjects receiving Eylea (23.9%) (presumably from week 20) up to Week 52, which is partially attributed to more optional doses received after a missed planned dose in patients in the MYL-1701P arm, rather than worsening of their condition. A slightly higher proportion of subjects in the Eylea arm received less than 9 planned doses. Reassuringly, analyses of BCVA and CRT over time on the ITT and PP sets support the conclusion that missed and/or additional doses had no relevant impact on efficacy.

Ancillary analyses

Additional Sensitivity Analysis of Primary Endpoint

The following additional sensitivity analyses were performed on the primary endpoint:

- Analysis of the primary endpoint in which BCVA values after discontinuing study medication (i.e., values with an assessment date after the last study medication date) were excluded.
- Analysis of the primary endpoint in which missing BCVA values at Week 8 were replaced by LOCF approach using the analysis of covariance (ANCOVA) model.
- Tipping point analysis for delta method using multiple imputation.

Summary tables of sensitivity analyses are provided in Table 15 - Table 16. The results of these sensitivity analyses showed equivalence between the 2 treatment arms based on confidence intervals within the pre-specified equivalence range.

Table 15: Analysis of Mean Chane in BCVA from Baseline to Week 8 by MMRM Excluding Values after Discontinuing Study Medication ITT Set

Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)
Visit 5 (Week 8) – PRIMARY ENDPOINT		
Subjects with value at baseline and this week	162	164
Adjusted mean (SE)	6.59 (0.547)	6.60 (0.546)
90% CI	(5.68, 7.49)	(5.70, 7.51)
95% CI	(5.51, 7.66)	(5.53, 7.68)
Adjusted mean difference (SE)		-0.02 (0.728)
90% CI		(-1.22, 1.18)
95% CI		(-1.45, 1.41)

Results for differences displayed in Eylea®-column, difference defined as MYL-1701P minus Eylea.
N=number of subjects in the treatment group analysis set. [a] Statistics are from a linear mixed model for repeated measures including treatment, Visit, Treatment*Visit and Region as fixed effects with baseline BCVA as a covariate. The unstructured co-variance matrix was used to adjust for the within-subject error variance. Estimation will use restricted maximum likelihood, and the denominator degrees of freedom will use the Kenward-Roger estimate. CI=Confidence interval, SE=Standard error.
Source: Table 14.2.1.2a of MYL-1701P-3001, 52-Week CSR

Table 16: Analysis of Mean Change in BCVA from Baseline to Week 8 by Analysis of Covariance (ANCOVA) using LOCF Approach – ITT Set

Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)
Visit 5 (Week 8)		
Subjects with value at baseline and this week	171	172
Adjusted mean (SE)	6.34 (0.548)	6.31 (0.549)
90% CI	(5.44, 7.25)	(5.40, 7.21)
95% CI	(5.27, 7.42)	(5.23, 7.39)
Adjusted mean difference (SE)		0.04 (0.722)
90% CI		(-1.16, 1.23)
95% CI		(-1.38, 1.46)

While the LOCF imputation used for the above sensitivity analyses is not considered conservative for the hypothesis of equivalence testing and does therefore not provide strong additional support in favour of equivalence, the results of the tipping point analysis indicate that the results are sufficiently robust. The results of this tipping point analysis are summarized in Table 17. Results were tipped from equivalent to not equivalent only for extreme assumptions such as when the imputed BCVA values were made better by at least 10 letters for Eylea and worse by at least 10 letters for MYL-1701P or vice versa as well as when the imputed BCVA values were made better by 5 letters for Eylea and worse by 15 letters for MYL-1701P. Given the treatment effect profile from observed data and considering 5 letters constitute one complete line in the ETDRS chart, these imputed values are considered unlikely to represent the unmeasured true values, and hence the primary analysis result and the conclusion of equivalence of the two treatment arms in the primary endpoint is supported.

Table 17: Analysis of Mean Change in BCVA from Baseline to Week 8 by Tipping point Analysis – ITT Set

	Shift with MYL-1701P					
Shift with Eylea	10	5	0	-5	-10	-15
10	0.35 (-1.17, 1.87)	-0.10 (-1.58, 1.38)	-0.55 (-2.03, 0.92)	-1.01 (-2.50, 0.48)	**-1.46 (-3.00, 0.08)**	**-1.92 (-3.53, -0.31)**
5	0.64 (-0.83, 2.12)	0.15 (-1.29, 1.58)	-0.31 (-1.74, 1.12)	-0.76 (-2.21, 0.69)	-1.22 (-2.71, 0.28)	**-1.67 (-3.24, -0.10)**
0	0.94 (-0.52, 2.41)	0.45 (-0.98, 1.87)	-0.01 (-1.42, 1.41)	-0.46 (-1.89, 0.97)	-0.91 (-2.39, 0.57)	-1.37 (-2.92, 0.19)
-5	1.25 (-0.22, 2.72)	0.75 (-0.68, 2.18)	0.29 (-1.12, 1.71)	-0.16 (-1.59, 1.28)	-0.61 (-2.09, 0.87)	-1.07 (-2.62, 0.49)
-10	**1.55 (0.05, 3.05)**	1.05 (-0.41, 2.51)	0.60 (-0.85, 2.04)	0.14 (-1.32, 1.60)	-0.31 (-1.82, 1.19)	-0.77 (-2.34, 0.81)
-15	**1.85 (0.30, 3.40)**	1.35 (-0.15, 2.85)	0.90 (-0.59, 2.39)	0.44 (-1.06, 1.95)	-0.01 (-1.56, 1.53)	-0.46 (-2.08, 1.15)

Estimates and 95% CIs for the treatment difference defined as MYL-1701P minus Eylea from the tipping point analysis are displayed. CI=Confidence interval.
Source: Table 14.2.1.4.1a of MYL-1701P-3001, 52-Week CSR

Additional Sensitivity and Supplementary Analyses to Assess the Impact of COVID-19-Related Disruption

The following additional sensitivity and supplementary analyses were done to assess the impact of COVID-19-related disruptions on the primary analysis:

- Primary analysis repeated with COVID-19-related delayed BCVA assessments treated as missing [Mean difference (SE): 0.03 (0.736); 95% CI: -1.42, 1.47].
- Primary analysis repeated without the subjects who are impacted by COVID-19 based on the 3 criteria defined in the protocol, namely
    - Missed study drug administration at Visit 4/Week 4 because of the COVID-19 pandemic
    - Missed BCVA examination for the study eye at Visit 5/Week 8 because of the COVID-19 pandemic

- Delayed BCVA examination for the study eye at Visit 5/Week 8 by more than 7 days from scheduled visit date because of the COVID-19 pandemic, with scheduled date defined as 28 days from the study drug administration at Visit 4/Week 4

[Analysis of Mean Change in BCVA (letters) from Baseline to Week 8: Adjusted Mean difference between the treatment groups: 0.13; 95% CI: -1.32, 1.58]

- A tipping point analysis where only non-pandemic related missing data were tipped and standard missing at random imputation was used for COVID-19 related missing data (Table 18).

Table 18: Analysis of Mean Change in BCVA from Baseline to Week 8 by Tipping Point Analysis Based Only on Non-pandemic Related Missing Data and Standard Missing at Random Imputation for COVID-19 Related Missing Data – ITT Analysis Set

	Shift with MYL-1701P					
Shift with Eylea	1.0	5	0	-5	-10	-15
10	0.17 (-1.27, 1.61)	0.03 (-1.40, 1.46)	-0.11 (-1.54, 1.31)	-0.26 (-1.69, 1.18)	-0.40 (-1.85, 1.06)	-0.54 (-2.03, 0.94)
5	0.22 (-1.21, 1.65)	0.08 (-1.34, 1.50)	-0.06 (-1.48, 1.36)	-0.20 (-1.63, 1.22)	-0.34 (-1.79, 1.10)	-0.49 (-1.96, 0.99)
0	0.28 (-1.15, 1.70)	0.14 (-1.28, 1.55)	-0.01 (-1.42, 1.41)	-0.15 (-1.57, 1.27)	-0.29 (-1.73, 1.15)	-0.43 (-1.91, 1.04)
-5	0.33 (-1.09, 1.76)	0.19 (-1.22, 1.60)	0.05 (-1.37, 1.46)	-0.10 (-1.52, 1.33)	-0.24 (-1.68, 1.20)	-0.38 (-1.85, 1.09)
-10	0.39 (-1.04, 1.81)	0.24 (-1.17, 1.66)	0.10 (-1.32, 1.52)	-0.04 (-1.47, 1.38)	-0.18 (-1.63, 1.26)	-0.33 (-1.80, 1.15)
-15	0.44 (-1.00, 1.88)	0.30 (-1.13, 1.72)	0.15 (-1.27, 1.58)	0.01 (-1.42, 1.45)	-0.13 (-1.58, 1.32)	-0.27 (-1.76, 1.21)

- Subgroup analysis based on subgroups defined by enrolment period (randomized before 25 Jan 2020, randomized on or after 25 Jan 2020), with 25 Jan 2020 chosen as cut-off as it was the earliest randomization date for subjects who reported any COVID-19 pandemic related protocol deviation until the Week 8 visit based on the deviation description in the protocol deviation CTMS file from 19 Aug 2020 (Table 19).

Table 19: Analysis of Mean Change in BCVA from Baseline to Week 8 by MMRM by Enrolment Period – ITT Analysis Set

Enrolment Period	Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)
Subjects randomized before 25-Jan-2020	Total number of subjects (m)	115	113
	Visit 5 (Week 8)		
	Subjects with value at baseline and this week	113	112
	Adjusted mean (SE)	7.14 (0.671)	6.83 (0.674)
	90% CI	(6.03, 8.25)	(5.72, 7.94)
	95% CI	(5.82, 8.46)	(5.51, 8.16)
	Adjusted mean difference (SE)		0.31 (0.869)
	90% CI		(-1.13, 1.74)
	95% CI		(-1.41, 2.02)
Subjects randomized on or after 25-Jan-2020	Total number of subjects (m)	64	63
	Visit 5 (Week 8)		
	Subjects with value at baseline and this week	50	53
	Adjusted mean (SE)	5.46 (1.041)	5.90 (1.031)
	90% CI	(3.74, 7.19)	(4.19, 7.61)
	95% CI	(3.40, 7.52)	(3.86, 7.95)
	Adjusted mean difference (SE)		-0.44 (1.324)
	90% CI		(-2.64, 1.75)
	95% CI		(-3.06, 2.18)

Demographic and baseline characteristics were comparable between subjects randomized before 25 Jan 2020, and subjects randomized on or after 25 Jan 2020, except a considerably lower proportion of overall enrolled subjects from the US (23.7% before vs 7.1% on or after 25 Jan 2020), while more patients were recruited from the rest of the world (i.e. India: 11.8% before vs 39.4% on or after 25 Jan 2020). As a likely consequence, the overall proportion of Asian participants increased (24.1% before vs 51.2% on or after 25 Jan 2020), but distribution between treatment arms was not affected.

However, upon analysis of subjects randomized on or after 25 Jan 2020 only, the adjusted mean change in BCVA at Week 8 was lower than what would be expected (5.46 and 5.90 in the MYL-1701P and Eylea group, respectively). Upon request, the Applicant explained that in previous clinical studies the Japanese population also had a lower mean response compared to the overall population after 8 weeks. In fact, the lower mean change in BCVA in those subgroups points toward geographic and/or ethnic differences regarding the treatment effect, even after extended treatment (Week 52) [Terasaki H et al 2019]. Nevertheless, in the current study MYL-1701P-3001 the sensitivity to demonstrate biosimilarity is not considered compromised, since the distribution of patients from Japan and India was balanced between treatment arms in both randomization periods, and since at the timepoint for primary assessment (Week 8) the mean change in BCVA has not yet reached the plateau for maximal treatment effect. Although the 95% CI of mean treatment difference in subjects randomized on or after 25 Jan 2020 [-3.06, 2.18] was slightly outside the equivalence range [-3, +3], no concern regarding biosimilarity is raised, as this subgroup was overall considerably smaller and lacks statistical precision.

The 95% CIs for the treatment difference of mean changes from Baseline to Week 8 for BCVA from the analysis with COVID-19 related delayed assessments treated as missing data and the analysis without the subjects impacted by COVID-19 based on the defined criteria, respectively, were fully contained within the interval of [-3, +3] letters and the analyses supported the primary analysis.

The tipping point analysis where only non-pandemic related missing data were tipped and standard missing at random imputation was used for COVID-19 related missing data revealed that no results were tipped from equivalent to not equivalent in this case. The most extreme scenarios considered, i.e. when the imputed BCVA values were made better by 10 letters or worse by 15 letters for either treatment arm, are already considered extremely unrealistic and therefore fully sufficient to support robustness of the results with this respect.

Subgroup Analyses for Primary Efficacy Endpoint

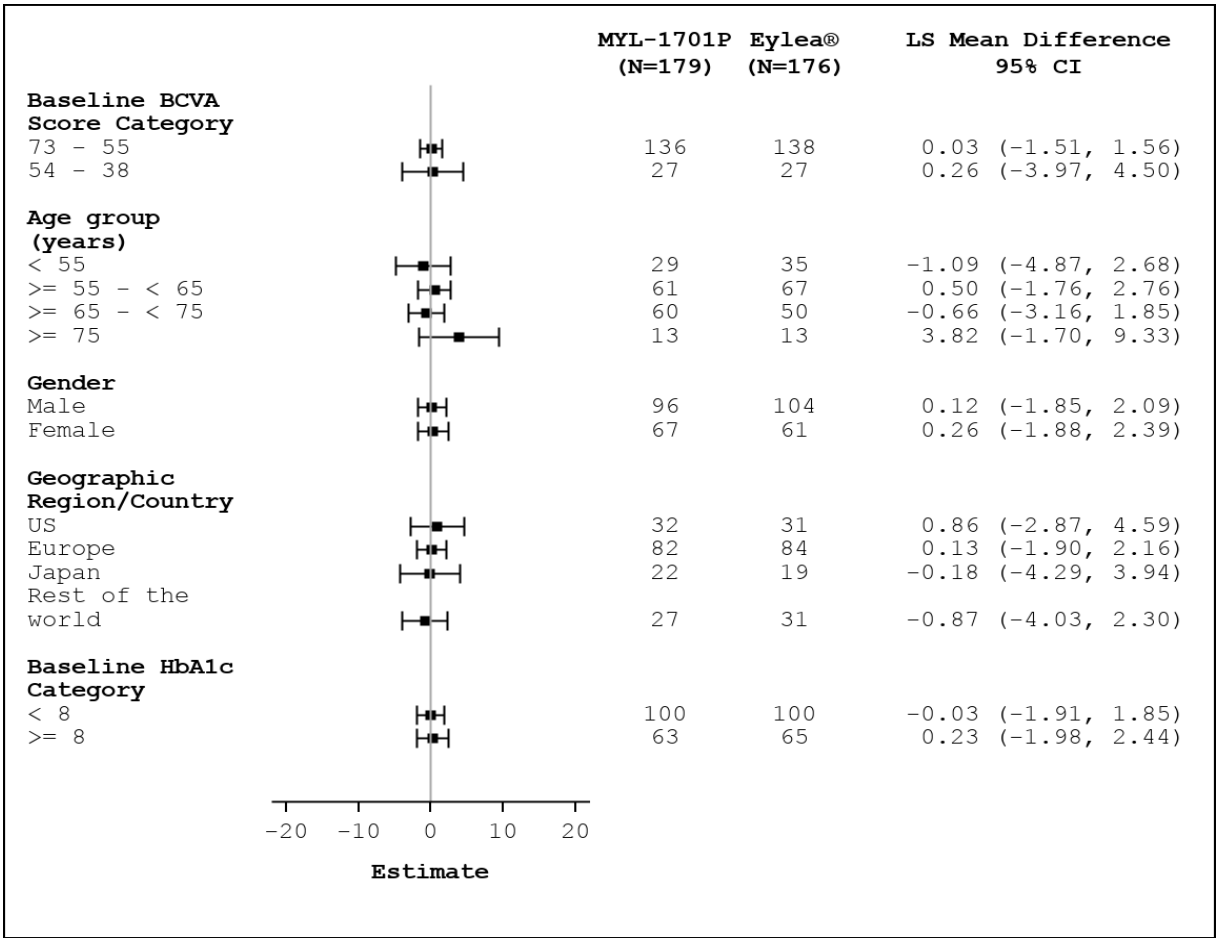
The Forest plot of all subgroup analyses (ITT analysis) for mean change in BCVA from baseline to Week 8 (Observed Data) with 95% CI is provided in Figure 4. Subgroup analyses for any anti-VEGF therapy in fellow eye prior to visit 5/Week 8 (Yes, No) and ADA status (positive, negative) are shown in Table 20 and Table 21, respectively.

Overall, the analyses revealed that mean change in BCVA from baseline to Week 8 by subgroups continues to support equivalence between the treatment arms. In some subgroups, the sample size was too small for a meaningful analysis and led to wide CIs, not allowing conclusions on these.

BCVA at baseline is informative for the room for improvement. A lower magnitude of change from baseline may be expected in patients with higher baseline BCVA. Indeed, the adjusted mean change in BCVA at Week 8 was lower in the BCVA subgroup 73-55 (6.24 [MYL-1701P] and 6.21 [Eylea]) compared to the 54-38 subgroup (7.95 [MYL-1701P] and 7.69 [Eylea]. On the other hand, assessment of decreases in visual acuity may be difficult in patients with already low baseline BCVA. Upon request, the Applicant provided a separate subgroup analysis for baseline BCVA 50-69, a range which would allow sufficient room for improvement or deterioration and which is thus considered more sensitive. Importantly, in the most sensitive subgroup of subjects with baseline BCVA 50-69, the treatment effect was similar to the primary analysis of the overall study population. The mean treatment difference was -0.01 and the 95% CI was [-1.89, 1.86] and therefore within the pre-defined equivalence range of [-3, +3] letters. This subgroup was also the largest (114 subjects in MYL-1701P and 106 subjects in Eylea) and is therefore considered the most relevant in this biosimilar exercise. Unexpectedly, the BCVA change at Week 8 was comparable in magnitude (MYL-1701P: 7.05; Eylea: 6.31) in the highest baseline BCVA group of 70-73 compared to the overall population (MYL-1701P: 6.60; Eylea: 6.56). Nevertheless, the concern of limited room for improvement is reflected in the key secondary endpoint CRT change at Week 8, which was below the expected improvement for this subgroup (MYL-1701P: -76.67; Eylea: -103.23 vs. overall population: MYL-1701P: -112.15; Eylea: -123.61).

Finally, a comparably high adjusted mean difference (3.82) was observed in the subgroup of >=75 year olds. This was mainly driven by an unusually low adjusted mean change in BCVA in the Eylea treatment group (3.19). As the subgroup was rather small (n = 13 in each treatment arm) and the 95% CI as expected very wide, this observation is eventually of no concern.

Note: For BCVA, baseline is defined as the last observation prior to or on the date of the first dose of study drug.



Change from baseline was analyzed using analysis of MMRM. See details of MMRM model in Tables 14.2.1.5.1.1a to 14.2.1.5.1.7a. N/A=Not applicable. Source: Listing 16.2.4.1a, 16.2.6.5a, 16.2.8a, Figure 14.2.1.1a

Figure 7. Forest Plot for Statistical Analysis of Mean Change in BCVA from Baseline to Week 8 by Subgroups (Observed Data; 95% CI) – ITT Set

Table 20: Analysis of Mean Change from Baseline at Week 8 for Best Corrected Visual Acuity (BCVA) by Mixed Model Repeated Measures (MMRM) by Any Anti-VEGF Therapy in Fellow Eye Prior to Visit 5 (Week 8) ITT Analysis Set

Any Anti-VGEF Therapy in Fellow Eye Prior to Visit 5 (Week 8)	Statistics [a]	MYL-1701P (N=179)	Eylea® (N=176)
Yes	Total number of subjects (m)	24	36
	Visit 5 (Week 8)		
	Subjects with value at baseline and this week	23	36
	Adjusted mean (SE)	4.05 (2.237)	5.98 (1.888)
	90% CI	(0.32, 7.79)	(2.82, 9.13)
	95% CI	(-0.42, 8.53)	(2.20, 9.76)
	Adjusted mean difference (SE)		-1.92 (1.945)
	90% CI		(-5.18, 1.33)
	95% CI		(-5.82, 1.98)
No	Total number of subjects (m)	155	140
	Visit 5 (Week 8)		
	Subjects with value at baseline and this week	140	129
	Adjusted mean (SE)	6.90 (0.601)	6.68 (0.629)
	90% CI	(5.90, 7.89)	(5.64, 7.72)
	95% CI	(5.71, 8.08)	(5.44, 7.92)
	Adjusted mean difference (SE)		0.21 (0.790)
	90% CI		(-1.09, 1.52)
	95% CI		(-1.34, 1.77)

Table 21: Mean Change in BCVA (ETDRS letters) from Baseline to Week 52 by ADA Status – ITT Set

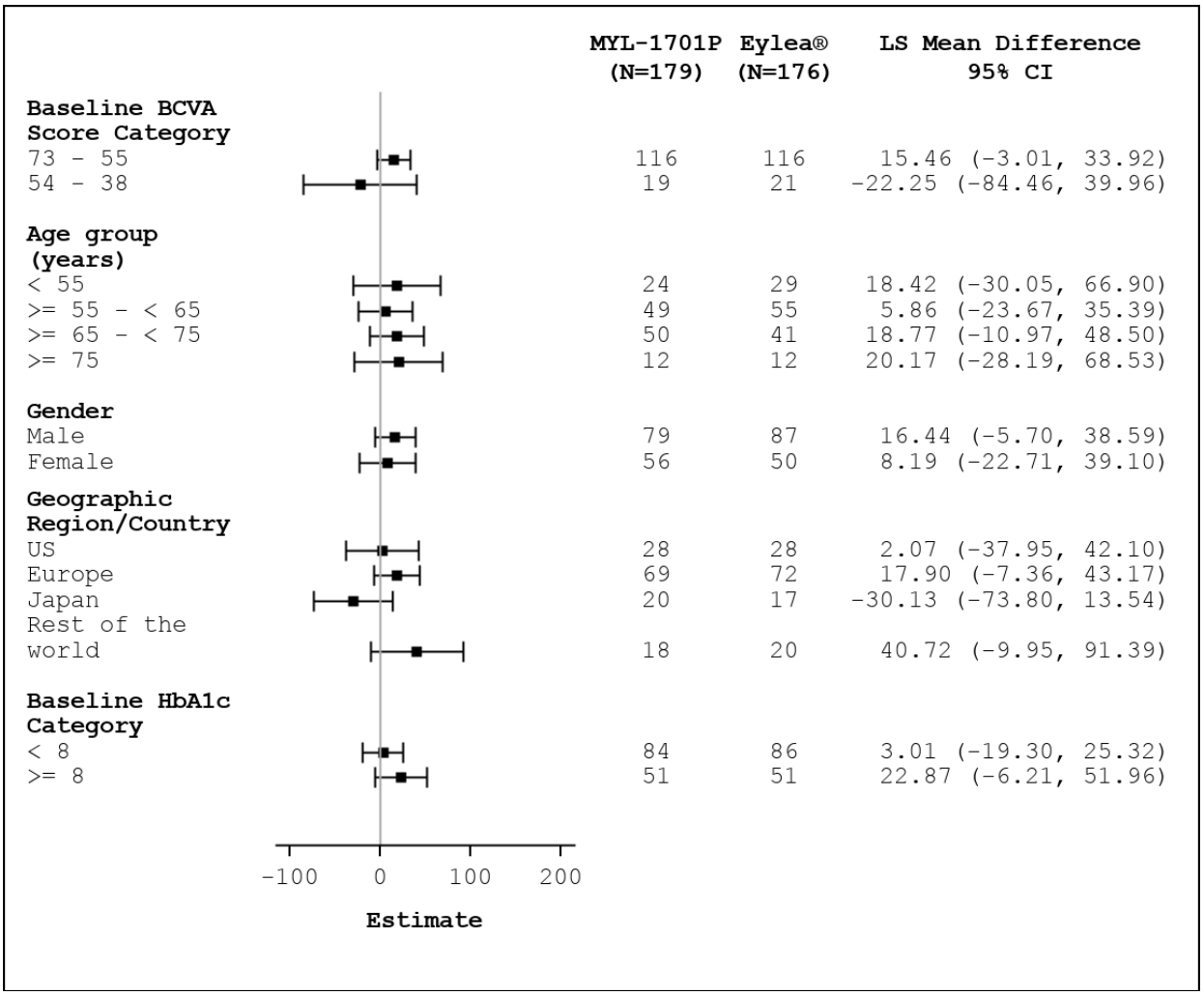
	ADA positive		ADA negative	
Timepoints	MYL-1701P Mean (SD); n	Eylea Mean (SD); n	MYL-1701P Mean (SD); m	Eylea Mean (SD); m
V4 (Week 4)	7.60 (5.950); 15	5.77 (5.354); 22	4.83 (6.895); 156	5.17 (6.000); 150
V5 (Week 8)	8.20 (6.826); 15	8.14 (5.685); 22	6.89 (7.017); 148	6.62 (6.656); 143
V7 (Week 16)	12.20 (5.557); 15	8.82 (6.192); 22	8.76 (7.548); 139	8.91 (6.729); 141
V9 (Week 24)	11.88 (6.800); 17	10.30 (5.235); 23	9.93 (8.105); 136	8.72 (8.158); 135
V11 (Week 32)	10.42 (6.963); 19	11.78 (7.064); 23	10.76 (7.918); 130	9.97 (7.567); 137
V13 (Week 40)	10.75 (6.282); 20	10.71 (5.967); 24	10.25 (8.653); 131	10.04 (8.748); 135
V16 (Week 52)	11.25 (8.175); 20	10.85 (5.998); 26	11.33 (8.997); 141	10.53 (8.663); 132

N/A=Not applicable; SD=Standard deviation. n=number of subjects who reported ADA positive at any visit (including baseline) until that visit in ADA positive subgroup; m=number of subjects who did not report ADA positive at any visit (including baseline) until that visit in ADA negative subgroup.
Source: Table 14.2.1.7.1b and Listing 16.2.6.5b, 16.2.9.4b

It appears that neither BCVA change from baseline nor equivalence was compromised by the occurrence of ADA. In fact, at Week 8 the mean change from baseline in BCVA was even higher and very similar in both treatment arms in the ADA positive subgroup in a descriptive analysis. However, due to the rather small subgroup of ADA positive subjects (n = 15 in the MYL-1701P and n = 22 in the Eylea arms), these results need to be interpreted with caution. For completeness, subgroup analyses, including adjusted mean differences and corresponding CIs, were provided for mean change from baseline of BCVA at week 8 and for the key secondary endpoint (mean change from baseline in CRT at Week 8). As expected, it was concluded that the occurrence of ADA did not have an impact on efficacy or PD aspects of aflibercept.

Ancillary Analyses for Secondary Efficacy Endpoints

The mean change in CRT (ITT analysis) from baseline to week-8 in subgroups (observed data) with 95% CI is provided in Figure 8. Again, in some subgroups, the sample size was too small for a meaningful analysis and led to wide CIs. Yet, biosimilarity is also supported by these analyses, since similar results were observed.



CRT = Central Retinal Thickness. Note: For CRT, baseline is defined as the last observation prior to or on the date of the first dose of study drug. CRT was measured as central subfield thickness. Change from baseline was analyzed using analysis of MMRM. See details of MMRM model in Tables 14.2.2.3.1.1a to 14.2.2.3.1.7a. N/A=Not applicable. Source: Listing 16.2.4.1a, 16.2.6.2a, 16.2.6.5a, 16.2.8a, Figure 14.2.2.1a

Figure 8. Forest Plot for Statistical Analysis on Mean Change in CRT (µm) from *Baseline to Week 8 by Subgroups (Observed Data; 95% CI) – ITT Set*

For mean change from baseline in CRT over time, additional analyses were performed using:

- Central reading including indeterminate values - The secondary analysis utilizing the central reader CRT values did not consider the values that were flagged as indeterminate. All the SD-OCT images for the study eye were transmitted to the independent central reading center. The central reader reviewed and reported the CRT values. According to their standard operating procedures, the central reader would have indicated a CRT value as "indeterminate" in cases where the SD-OCT images had some quality issue such as poor segmentation or centering. Such "indeterminate" CRT values were recorded in a separate field by the central reader. An additional analysis was performed by including such indeterminate values from the central reading (Figure 9).
- Investigator assessment – According to final SAP version 3.0, for the analysis of the secondary endpoint, mean change from baseline in CRT, only the central reading was considered and, the CRT values provided by the Investigators based on their evaluation of the SD-OCT scan images

were not considered. The Investigators independently evaluated the SD-OCT scan images at all the visits and recorded the CRT values. An additional analysis was performed utilizing the CRT values recorded by the Investigators based on their assessment (Figure 10).

In these additional analyses, the mean change from baseline in CRT over time was comparable between the treatment arms. The results from the additional analyses are comparable with the secondary endpoint analysis, further supporting biosimilarity.

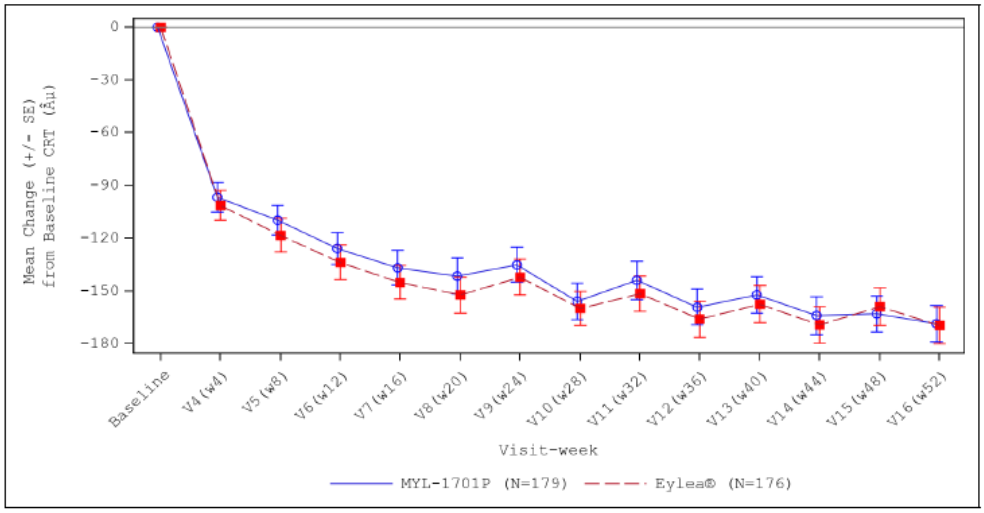


Figure 9. Line Plot for Mean Change from Baseline for CRT (µm) Reading from DARC (including Indeterminate Values) – ITT Set

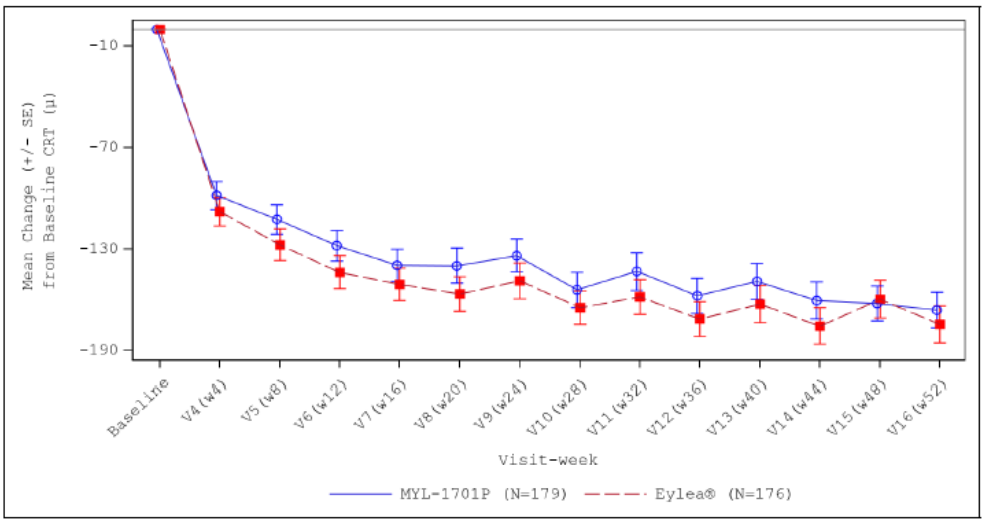


Figure 10. Line Plot for Mean Change from Baseline for CRT (µm) from Investigator Assessments – ITT Set

In order to assess whether the extra 31 subjects randomized due to COVID-19 criteria could have affected any of the outcomes, the Applicant provided results of analyses for the primary and key secondary variable including only the number of patients as initially planned, i.e. the first 324 patients randomized, upon request. These analyses indicate that the results were similar to the results of all 355 subjects, confirming that the data of 31 additional subjects did not have an impact on study outcomes. Furthermore, the distribution of those extra subjects was balanced between the treatment arms (n = 17 in MYL-1701P arm; n = 14 in Eylea arm).

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 22: Summary of efficacy for trial MYL-1701P-3001

Title: A Multi Center, Randomized, Double-Masked, Active-Controlled, Comparative Clinical Study to Evaluate the Efficacy and Safety of MYL-1701P and Eylea in Subjects with Diabetic Macular Edema			
Study identifier	NCT No.: NCT03610646 EudraCT No.: 2017-004358-40 IND Number: 131320		
Design	Multi-center, 1:1 randomized, double masked, active controlled, comparative clinical study to evaluate the efficacy, safety, PK and immunogenicity between MYL-1701P and US-licensed Eylea in subjects with diabetic macular edema (DME) treated up to 52 weeks.		
	Duration of main phase:	23 Aug 2018 – 10 Sep 2021	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	not applicable	
Hypothesis	Equivalence		
Treatment groups	MYL-1701P (M710) (a proposed biosimilar to aflibercept)	2 mg (0.05 mL) aflibercept intravitreal injection every 4 weeks for a total of 5 injections, and then every 8 weeks up to Week 48 (9 doses in total, with optional doses to continue at every 4 weeks), n = 179	
	Eylea (USA sourced)	2 mg (0.05 mL) aflibercept intravitreal injection every 4 weeks for a total of 5 injections, and then every 8 weeks up to Week 48 (9 doses in total, with optional doses to continue at every 4 weeks), n = 176	
Endpoints and definitions	Primary endpoint	Mean change from baseline in BCVA (ETDRS letter score) at Week 8	Clinical equivalence is demonstrated if the two-sided 95% CI of the adjusted mean difference of the mean change from baseline in BCVA at Week 8 is contained within the pre-defined equivalence range [-3, +3] letters
	Key secondary endpoint	Mean change from baseline in CRT as determined by SD-OCT over time	The adjusted mean difference of the mean change from baseline in CRT as determined by SD-OCT at Week 8 and over time is considered a PD aspect of aflibercept and supportive to demonstrate clinical equivalence. No equivalence range has been pre-defined.
	Other secondary efficacy endpoints	Mean change in BCVA over time	
		Proportion of subjects who gained ⩾15 letters over time	
		Number of injections of study drug administered during the study period	
Database lock	10 Sep 2021		
Results and Analysis			
Analysis description	**Primary Analysis: Change from baseline in BCVA at Week 8 (ITT/FAS)**		
Analysis population and time point description	Intent to treat (ITT): all randomized subjects Full analysis set (FAS): ITT subjects who received any study drug, who had a baseline BCVA, and who also had at least one post dosing BCVA assessment up to Week 8		
Descriptive statistics	Treatment group	MYL-1701P	Eylea

and estimate variability	Number of subjects*	179 (ITT) 171 (FAS)	176 (ITT) 172 (FAS)
	Change from baseline in BCVA at Week 8 Mean (SE) (ETDRS letter score) (ITT/FAS‡)	6.60 (0.548)	6.56 (0.548)
Effect estimate per comparison	Primary endpoint: **Change from baseline in BCVA at Week 8** ‡	Comparison groups	MYL-1701P vs Eylea
		Mean difference (SE)	0.04 (0.730)
		95% confidence interval for difference	[-1.40, 1.47]
Notes	Clinical equivalence is demonstrated if the two-sided 95% CI of the adjusted mean difference of the mean change from baseline in BCVA at Week 8 is contained within the pre-defined equivalence range [-3, +3] letters		
Analysis description	**Primary Analysis: Change from baseline in BCVA at Week 8 (PP)**		
Analysis population and time point description	Per protocol (PP): FAS subjects who had no major protocol deviations Primary endpoint evaluation at Week 8		
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects*	165	161
	Change from baseline in BCVA at Week 8 Mean (SE) (ETDRS letter score) (PP)	6.61 (0.556)	6.80 (0.565)
Effect estimate per comparison	Primary endpoint: **Change from baseline in BCVA at Week 8**	Comparison groups	MYL-1701P vs Eylea
		Mean difference (SE)	-0.19 (0.745)
		95% confidence interval for difference	[-1.66, 1.27]
Notes	Clinical equivalence is demonstrated if the two-sided 95% CI of the adjusted mean difference of the mean change from baseline in BCVA at Week 8 is contained within the pre-defined equivalence range [-3, +3] letters		
Analysis description	**Key Secondary Analysis: Change from baseline in CRT over time**		
Analysis population and time point description	Intent to treat (ITT): all randomized subjects Secondary endpoint evaluations at Week 8 until Week 52		
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects*	179	176
	Change from baseline in CRT at Week 8 Mean (SE) (µm) (ITT)	-112.15 (6.742)	-123.61 (6.807)
Effect estimate per comparison	Key Secondary Endpoint: **Change from baseline in CRT at Week 8**	Comparison groups	MYL-1701P vs Eylea
		Mean difference (SE)	11.46 (8.986)
		95% confidence interval for difference	[-6.22, 29.14]
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects*	179	176
	Change from baseline in CRT at Week 24 Mean (SE) (µm) (ITT)	-130.68 (7.077)	-137.78 (7.064)
Effect estimate per comparison	Key Secondary Endpoint: **Change from baseline in CRT at Week 24**	Comparison groups	MYL-1701P vs Eylea
		Mean difference (SE)	7.10 (9.516)
		95% confidence interval for difference	[-11.59, 25.78]
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects*	179	176

	Change from baseline in CRT at Week 52 Mean (SE) (µm) (ITT)	-170.14 (7.198)	-167.67 (7.260)
Effect estimate per comparison	Key Secondary Endpoint: **Change from baseline in CRT at Week 52**	Comparison groups	MYL-1701P vs Eylea
		Mean difference (SE)	-2.47 (9.737)
		95% confidence interval for difference	[-21.59, 16.64]
Notes	The adjusted mean difference of the mean change from baseline in CRT as determined by SD-OCT at Week 8 and over time is considered a PD aspect of aflibercept and supportive to demonstrate clinical equivalence. No equivalence range has been pre-defined.		
Analysis description	**Other Secondary Analysis: Mean change in BCVA over time**		
Analysis population and time point description	Intent to treat (ITT): all randomized subjects Secondary endpoint evaluations until Week 52		
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects*	179	176
	Change from baseline in BCVA at Week 24 Mean (SE) (ETDRS letter score) (ITT)	9.33 (0.616)	8.61 (0.617)
Effect estimate per comparison	Other Secondary Endpoint: **Change from baseline in BCVA at Week 24**	Comparison groups	MYL-1701P vs Eylea
		Mean difference (SE)	0.72 (0.829)
		95% confidence interval for difference	[-0.90, 2.35]
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects*	179	176
	Change from baseline in BCVA at Week 52 Mean (SE) (ETDRS letter score) (ITT)	10.76 (0.619)	10.52 (0.621)
Effect estimate per comparison	Other Secondary Endpoint: **Change from baseline in BCVA at Week 52**	Comparison groups	MYL-1701P vs Eylea
		Mean difference (SE)	0.24 (0.834)
		95% confidence interval for difference	[-1.40, 1.88]
Analysis description	**Other Secondary Analysis: Proportion of subjects who gained ⩾15 letters**		
Analysis population and time point description	Intent to treat (ITT) Secondary endpoint evaluation at Week 52		
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects§	179	176
	Proportion of subjects who gained ⩾15 letters over time	33.0%	29.1%
Effect estimate per comparison	Other Secondary Endpoint: **Proportion of subjects who gained ⩾15 letters over time**	Comparison groups	MYL-1701P vs Eylea
		Mean difference	3.9%
Analysis description	**Other Secondary Analysis: Number of injections of study drug administered during the study period**		
Analysis population and time point description	Safety Set: subjects who received at least one dose of study drug Secondary endpoint evaluation at Week 52		
Descriptive statistics and estimate variability	Treatment group	MYL-1701P	Eylea
	Number of subjects	178	176
	Number of injections of study drug administered during the study period Mean (SD)	8.4 (2.06)	8.7 (1.76)

Effect estimate per comparison	Other Secondary Endpoint: **Number of injections of study drug administered during the study period**	Comparison groups	MYL-1701P vs Eylea
		Mean difference	-0.3

* Missing values were addressed using an MMRM.
‡ Currently, the number of subjects with available values at this time point in the ITT and FAS is identical (MYL-1701P: n = 163; Eylea: n = 165) and therefore the results for the primary analysis are identical.
§ Missing values were replaced by LOCF.

2.4.5. Discussion on clinical efficacy

Design and conduct of clinical studies

For the clinical development program to demonstrate biosimilarity of the biosimilar Yesafili (MYL-1701P; M710) and the reference product US-sourced Eylea, one single pivotal phase 3 study (MYL-1701P-3001) has been performed.

Study MYL-1701P-3001 was a multicenter, randomized, double masked, active controlled, comparative clinical study to demonstrate that no clinically meaningful differences exist between MYL-1701P and US-licensed Eylea regarding efficacy, safety, and immunogenicity in subjects with Diabetic Macular Edema (DME). No dedicated human PK or PD studies were conducted. Instead, supportive PK analyses were conducted in a subset of patients enrolled in MYL-1701P-3001. This strategy was agreed, since systemic exposure after intravitreal injection is expected to be low, and due to ethical concerns.

Study MYL-1701P-3001 enrolled subjects with DME following type 1 or type 2 diabetes mellitus, with baseline CRT of ≥300 µm and BCVA at 4 m from 73 to 38 letters (ETDRS chart) equivalent to Snellen visual acuity of 20/40 to 20/200 in the study eye. Subjects with type 1 or type 2 diabetes mellitus who present with central DME involvement in the study eye is considered a suitable study population to demonstrate clinical equivalence between MYL-1701P and US-Eylea. The variability for mean change in BCVA was found to be lower in DME compared to neovascular (wet) age-related macular degeneration (wAMD) based on previous clinical studies of Eylea. The selection of patients with DME as study population is agreed.

It was recommended to include a more impaired and homogeneous patient population regarding baseline CRT and BCVA. Nevertheless, the finally selected criteria are similar to registrational clinical trials for Eylea (VIVID/VISTA) and considered suitable, with the caveats that assessment of decreases in visual acuity may be difficult in legally blind patients, and there may be limited room for improvement in subjects with higher BCVA or lower CRT. Similarly, exclusion criteria are by large in accordance with registrational clinical trials for Eylea in DME.

Five consecutive monthly intravitreal injections, followed by bimonthly intravitreal injections of MYL-1701P and US-Eylea were planned until end of study at Week 52. Hence, treatment with biosimilar MYL-1701P and the originator Eylea were in line with the SmPC of Eylea for DME treatment. The use of US-sourced Eylea as reference product is acceptable, as robust equivalence was demonstrated on the quality level. The study duration (52 weeks) is considered long enough to investigate the efficacy and safety profile of the product.

The primary endpoint, BCVA as assessed by ETDRS letters at Week 8, is suitable to demonstrate equivalence of clinical efficacy in patients with DME. The mean change from baseline in BCVA is considered a sufficiently sensitive endpoint that allows detection of the product-related differences. The

primary endpoint BCVA, measured using the ETDRS charts, is a validated and continuous metric which captures macular function well and is a suitable outcome measure. An early 2-month (8 weeks) time point is considered sensitive to detect eventual differences between the treatments and also minimizes the impact of potential confounding factors occurring later in the study.

The key secondary efficacy endpoint, mean change in CRT determined by SD-OCT over time, is considered adequate to reflect PD aspects of aflibercept. Other secondary efficacy endpoints aim to assess the maintenance of efficacy over time and are endorsed.

For the primary endpoint assessment, the predefined and accepted equivalence range to demonstrate biosimilarity was -3 to +3 letters. No equivalence range was defined for secondary endpoints. From a methodological perspective, the overall approach on the primary analyses and sensitivity analyses is considered adequate. Some additional analyses were requested to further support robustness of the results. Consequently, the Applicant provided analyses of the primary and secondary endpoints including only the number of patients initially planned, to ensure that the additionally recruited patients based on decisions during the study on missed/delayed dosing and/or study assessments because of the coronavirus disease 2019 (COVID-19) pandemic (as per protocol V 3.0) did not affect any of the outcomes. This ensured that the recruitment was not motivated by data-driven decisions that may have impacted the study interpretation. In addition and due to an inadequately chosen missing data handling strategy, the Applicant provided additional analyses on the secondary endpoint of the proportion of patients who gained or lost a letter.

In total, 355 patients were randomized 1:1 to receive MYL-1701P or Eylea. No patients discontinued the study due to any of the pre-specified COVID-19 criteria (Protocol Version 3.0). In general, protocol amendments were made to address the potential impact of the COVID-19 pandemic and to facilitate recruitment or to meet local legal requirements, which is considered appropriate to ensure conduct of the study.

Overall, the Applicant's clinical development program to demonstrate biosimilarity between MYL-1701P and US-Eylea with respect to efficacy is considered adequate to support this Application. The study design, study population, inclusion/exclusion criteria, and dose regimen were selected based on registrational studies for Eylea, are in line with the guidance on similar biological products, and were largely in compliance with Scientific Advice obtained.

Efficacy data and additional analyses

Primary assessment was presented for the ITT and PP analysis sets, which are considered equally important for the demonstration of biosimilarity by the Rapporteur. Although the Applicant presented the PP analysis set in the section *Sensitivity Analysis of Primary Endpoint*, all relevant data were available and appropriately summarized for assessment. An additional analysis on the FAS was also presented, but this comprised the same set of patients with available values at the timepoint of the primary analysis and results were identical to the ITT analysis. In this analysis, missing values were addressed by using an MMRM.

In the ITT Set, the primary endpoint mean (SE) change in BCVA from Baseline to Week 8 was 6.60 (0.548) and 6.56 (0.548) in the MYL-1701P and Eylea group, respectively. In both treatment groups, the effect size was what would be expected after treatment with aflibercept. The adjusted mean difference between the treatment groups was 0.04 and the 95% CI for the treatment difference was [-1.40, 1.47], which is within the predefined and accepted equivalence range of -3 to +3 letters.

In the PP Set, the mean (SE) change in BCVA from Baseline to Week 8 was 6.61 (0.556) and 6.80 (0.565) in the MYL-1701P and Eylea group, respectively. The adjusted mean difference was -0.19 and the 95% CI for the treatment difference was [-1.66, 1.27], which is also within the predefined and

accepted equivalence range of -3 to +3 letters. Thus, biosimilarity was demonstrated for the primary endpoint in the ITT and PP Analysis Sets.

To assess PD aspects of aflibercept, mean change in CRT over time was assessed as key secondary efficacy endpoint. At Week 8 mean (SE) change in CRT was -112.15 (6.742) µm and -123.61 (6.807) µm in the MYL-1701P and Eylea group, respectively. Again, in both treatment groups the change from baseline was what would be expected after treatment with aflibercept. Yet, the improvement was slightly more pronounced in the Eylea group, with an adjusted mean difference (SE) of 11.46 (8.986) µm. While an equivalence range was not defined for CRT, the 95% CI [-6.22 µm, 29.14 µm] indicated that there does not seem to be a relevant difference between the treatment groups. A difference of up to 50 µm is considered not clinically relevant, since in the present and other studies investigating anti-VEGF agents, an increase in CRT by ≥ 50 µm is defined as clinically relevant to trigger additional dosing. Hence, the observed minimally better improvement in the Eylea group (11.46 µm), as well as the estimated upper limit of the 95% CI (29.14 µm) are considered clearly below the established boundary for retreatment and therefore these changes are considered clinically irrelevant. Mean change in CRT throughout the entire study duration indicated an increase of improvement in both study arms over time. Overall, differences between study arms are considered small, as those are clearly below 50 µm, a change in CRT that would be considered clinically relevant. Hence, biosimilarity is supported by the results in this key secondary efficacy endpoint.

Other secondary endpoints included the mean change in BCVA over time up to Week 52 and the proportion of subjects who gained ≥15 letters at Week 52, both of which showed similar responses between both treatment groups, further supporting biosimilarity.

Per study protocol a total of nine injections were planned to be administered for the entire study duration of 52 weeks, with the option of receiving additional four doses upon worsening of BCVA or CRT. Although the median number of doses received was indeed nine injections in both treatment arms, the median of discrete numbers is an insensitive metric, and indeed only 56.3% of all patients received nine doses. Reassuringly, upon request it was clarified that only few of those patients received additional doses due to worsening of their condition, since the majority of patients who received 9 doses have not received any additional dose (95%). Of note, more patients (ITT set) in the MYL-1701P arm received additional doses of aflibercept (30.3%) compared to subjects receiving Eylea (23.9%), which is partially attributed to more optional doses received after a missed planned dose in patients in the MYL-1701P arm, rather than worsening of their condition. A slightly higher proportion of subjects in the Eylea arm received less than 9 planned doses. Reassuringly, analyses of BCVA and CRT over time on the ITT and PP sets support the conclusion that missed and/or additional doses had no relevant impact on efficacy.

To account for missing BCVA values, sensitivity analyses were conducted for the primary endpoint. The 95% CI for the adjusted mean differences between the two treatments from sensitivity analyses excluding BCVA values after discontinuing study medication (ITT Set) and replacing missing BCVA values by LOCF approach using the ANCOVA model (ITT Set) were similar to the primary outcome and well within the predefined equivalence range [-3, +3]. While the LOCF is not considered conservative for the hypothesis of equivalence testing and does therefore not provide strong additional support in favour of equivalence, the results of the tipping point analysis indicate that the results are sufficiently robust, since only extremely unfavourable and unrealistic assumptions for the missing values would tip the results towards non-equivalence, which is not considered a likely scenario for the unknown true values and therefore these results support robustness of the primary endpoint analysis and the conclusion on equivalence. Upon request, the Applicant also performed an additional analysis on the secondary endpoint "proportion of subjects who gained or lost letters" with an alternative imputation technique that utilized a multiple imputation method, indicating robustness of the results.

Additional sensitivity analyses were conducted to assess the impact of disruptions related to COVID-19. Demographic and baseline characteristics were comparable between subjects randomized before 25 Jan 2020, and subjects randomized on or after 25 Jan 2020, except a considerably lower proportion of overall enrolled subjects from the US (23.7% before vs 7.1% on or after 25 Jan 2020), while more patients were recruited from the rest of the world (i.e. India: 11.8% before vs 39.4% on or after 25 Jan 2020). As a likely consequence, the overall proportion of Asian participants increased (24.1% before vs 51.2% on or after 25 Jan 2020), but distribution between treatment arms was not affected.

Primary assessments considering COVID-19 related disruptions, such as missed or delayed examinations, showed that the 95% CI for the treatment difference was fully contained within the equivalence range [-3, +3]. However, upon analysis of subjects randomized on or after 25 Jan 2020 only, mean treatment difference was -0.44 and the 95% CI was [-3.06, 2.18]. Notably, the adjusted mean change in BCVA at Week 8 was lower than what would be expected (5.46 and 5.90 in the MYL-1701P and Eylea group, respectively). Upon request, the Applicant attributed this difference to an overall lower mean response previously reported in the Japanese population [Terasaki H et al 2019]. The sensitivity to demonstrate biosimilarity is not considered compromised in this subgroup, since the distribution of Asian patients was balanced between treatment arms in both randomization periods, and since at the timepoint for primary assessment (Week 8) the mean change in BCVA has not yet reached the plateau for maximal treatment effect.

Subgroup analyses for the primary efficacy endpoint supported equivalence between treatment arms, when the sample size was > 60 patients per group. In subgroup analyses with fewer subjects, 95% CIs were wider and not entirely contained within the equivalence range. Nevertheless, as the sample sizes were small and similar trends to the main analysis were observed, biosimilarity would still be supported.

At baseline, the majority (53.5%) of patients had BCVA of 65 or higher. As highlighted earlier, there may be limited room for improvement in patients with high BCVA and hence ceiling effects may affect assessment of biosimilarity. Indeed, the adjusted mean change in BCVA at Week 8 was lower in the BCVA subgroup 73-55 (6.24 [MYL-1701P] and 6.21 [Eylea]) compared to the 54-38 subgroup (7.95 [MYL-1701P] and 7.69 [Eylea]). On the other hand, assessment of decreases in visual acuity may be difficult in patients with already low baseline BCVA. Upon request, the Applicant showed a separate subgroup analysis for baseline BCVA 50-69, which would have been the preferred range, comprising a more heterogeneous and impaired population, which allows sufficient room for improvement or deterioration and is thus considered more sensitive. In this subgroup, the treatment effect was similar to the primary analysis of the overall study population. The mean treatment difference was -0.01 and the 95% CI was [-1.89, 1.86] and therefore within the pre-defined equivalence range of [-3, +3] letters. This subgroup was also the largest (114 subjects in MYL-1701P and 106 subjects in Eylea) and is therefore considered the most relevant in this biosimilar exercise.

It appears that neither the BCVA change from baseline nor equivalence was compromised by the occurrence of ADA. In fact, at Week 8 the mean change from baseline in BCVA was even higher and very similar in both treatment arms in the ADA positive subgroup. Likewise, no effect of ADA on PD aspects of aflibercept was observed, as mean change from baseline in CRT at Week 8 was also similar.

As would be expected due to low sample sizes, subgroup analyses for the key secondary efficacy endpoint (mean change in CRT at Week 8) resulted in wider 95% CIs compared to the main analysis. Yet, biosimilarity is supported since similar trends were observed.

Taken together, efficacy data show that MYL-1701P and US-Eylea can be regarded as equivalently efficacious based on pre-specified criteria of the primary endpoint. Biosimilarity is also supported by secondary endpoints and subgroup analyses.

Extrapolation of indications

In the EU, the reference product Eylea (aflibercept) is approved for treatment of wAMD, RVO, DME and myopic CNV in adults. The Applicant selected DME for the single phase 3 pivotal study (MYL-1701P-3001) and plans to obtain approval for DME and all other adults indications of Eylea, based on similar pathogenic mechanisms. The pathogenesis of all approved adults indications involves angiogenesis mediated by the members of the VEGF family of angiogenic factors, and the mechanism of action of aflibercept in DME is considered representative of the mechanism of action of aflibercept in all other adults approved indications for Eylea.

The justification presented by the Applicant to allow extrapolation from DME to all approved adults indications of Eylea is considered adequate, as analytical and clinical biosimilarity could be established.

2.4.6. Conclusions on the clinical efficacy

From an efficacy perspective, the clinical data suggest similarity between biosimilar Yesafili (MYL-1701P; M710) and the reference product US-Eylea.

2.4.7. Clinical safety

Safety Profile of the Reference Product Eylea

A complete overview of the undesirable effects of Eylea can be found in the Eylea SmPC.

Adverse events of particular concern include but are not limited to:

- Endophthalmitis and retinal detachment following intravitreal injections: In such an event, subject was instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- Increases in intraocular pressure after intravitreal injection.
- Potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

The most common adverse reactions (≥5%) reported in patients receiving Eylea were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

As this is a therapeutic protein, there is a potential for immunogenicity with Eylea/MYL-1701P. In registrational studies for Eylea (VIVID/VISTA) the incidence of pre-treatment immunoreactivity to VEGF Trap was approximately 1%-2.4% and the incidence of treatment-emergent immunoreactivity was approximately 1% at Week 52. Neutralizing antibodies occurred in 0.3-0.4%.

For any potential allergic reaction after administration of study drug, diagnosis and assessment of anaphylaxis was done using National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria of anaphylaxis.

Biosimilar MYL-1701P (M710)

All safety data for the biosimilar MYL-1701P (M710) are derived from pivotal phase 3 study MYL-1701P-3001, a multi-center, randomized, double-masked, active-controlled, comparative clinical study to evaluate the efficacy and safety of MYL-1701P and reference product US-Eylea in subjects with diabetic macular edema.

Considering the study dosed MYL-1701P for the first time in human subjects, a **Sentinel Cohort** Data Review Committee (SCDRC) was established for the safety evaluation of subjects enrolled into a

sentinel cohort. The sentinel cohort included 9 subjects, with at least 3 subjects receiving MYL-1701P. The study was to be continued only if no safety concerns arose from the sentinel cohort within the first week of dosing.

Safety variables in study MYL-1701P-3001:

Safety and tolerability were assessed over time which included ocular and non-ocular AEs, physical examination findings, ECG, vital signs measurements, and clinical laboratory tests evaluated at pre-specified time points (Table 23). Ocular safety was assessed using BCVA, SD-OCT, FA / FP, and complete ophthalmic examinations at pre-specified time points (Table 23).

Incidence, titer and neutralizing capacity of Anti-Drug Antibodies (ADA) were assessed as:

- **Treatment induced ADA**: ADA developed any time after the initiation of drug administration in a subject without pre-existing ADA.
- **Treatment boosted ADA**: any time after the initiation of drug administration the ADA titer was at least 4 times the baseline titer in a subject who had a pre-existing ADA at baseline.

Table 23: Study Schedule of Events

Assessment	Period	Screening	Treatment period																
	Visit	Screening Visit	V1/ BL	V2[a]	V3	V4	V5	V6	V7	V7A[p]	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Day or week:	D -28 to D -1	D1	D3 (±0 d)	W1 (±2d)	W4 (±3d)	W8 (±3d)	W12 (±7d)	W16 (±7 d)	W16 +2d (±0 d)	W20 (±7d)	W24 (±7d)	W28 (±7d)	W32 (±7d)	W36 (±7d)	W40 (±7d)	W44 (±7d)	W48 (±7d)	W52 (±7d) EOS/ ET
Informed Consent[a]		x																	
Demography		x																	
Medical, Surgical and Ophthalmic history[b]		x																	
Inclusion/Exclusion criteria		x	x																
Height/weight		x	x[c]																x[c]
Pregnancy test[d]		x	x			x	x	x	x		x	x	x	x	x	x	x	x	x
Clinical Safety Laboratory[e]		x	x		x			x				x							x
PT, aPTT and INR		x																	
PT, aPTT and INR for subjects in Czech Republic only		x						x				x			x			x	
Targeted Physical Examination[f]		x	x		x							x							x
Vital Signs[g]		x	x		x	x	x	x	x		x[h]	x	x[h]	x	x[h]	x	x[h]	x	x
12- Lead Electrocardiogram[i]		x	x		x							x							x
Complete Ophthalmologic Examination[j]		x	x	x[j]	x	x	x	x	x		x	x	x	x	x	x	x	x	x
Best Corrected Visual Acuity (Bilateral)		x	x			x	x	x	x		x	x	x	x	x	x	x	x	x
Spectral Domain – OCT / CRT		x	x			x	x	x	x		x	x	x	x	x	x	x	x	x
(Bilateral)																			
FA / FP (Bilateral)[k]		x																	x
Randomization[l]			x																
Study Drug administration			x			x	x	x	x		x[h]	x	x[h]	x	x[h]	x	x[h]	x	
Pharmacokinetic blood sampling[m]			x	x	x	x	x		x	x		x		x		x			x
Immunogenicity blood sampling[n]			x		x	x	x		x			x		x		x			x
Drug Tolerance blood sampling[n]			x		x	x	x		x			x		x		x			x
Adverse events[o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record Concomitant medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Diary Issue/Review[q]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: aPTT = activated partial thromboplastin time; BL = baseline visit; EOS = end of study; ET = Early Termination; INR = International Normalized Ratio
PT = Prothrombin Time
Note: An unscheduled visit may be necessary and can occur at any time if the Investigator believes it is essential for any reason

2.4.7.1. Patient exposure

Based on the review of data package of the first 9 subjects in the **sentinel cohort**, the SCDRC did not find any significant safety concern and concluded with consensus among committee members to continue recruitment.

Patient Disposition and Baseline Characteristics

Please refer to Section *Results –. Participant flow* and *Baseline data* for details.

Overall Extent of Exposure

Overall, 354 subjects (178 in the MYL-1701P arm and 176 in the Eylea arm), received study treatment. The median treatment duration was 364 days in both study arms. The mean (SD) number of doses received in each of the treatment arms was similar [8.4 (2.06) in MYL-1701P arm and 8.7 (1.76) in Eylea arm]. For more details see Table 3.

There were no dosing errors (such as wrong study drug treatment received) reported in this study. Of 355 randomized subjects, one subject randomized to the MYL-1701P arm withdrew consent to participate before receiving a dose of the study drug, and was therefore not included in the safety analysis set.

Safety analysis set (Safety Set)

The safety analysis set consisted of all subjects who received at least one dose of study drug. Subjects were included in the analysis according to the actual treatment received. The safety analysis set was the primary analysis set for safety analyses.

Table 24: Summary of Treatment Duration, Exposure to Study Medication and up to Week 52 – Safety Set

	MYL-1701P (N=178)	Eylea (N=176)	Overall (N=354)
Treatment duration (days) [a]			
Mean (SD)	338.3 (79.37)	346.4 (63.87)	342.3 (72.09)
Median	364.0	364.0	364.0
Min, Max	28, 386	28, 384	28, 386
Subjects completed all planned doses n (%)	136 (76.4)	128 (72.7)	264 (74.6)
Subjects completed at least one optional dose n (%)	54 (30.3)	42 (23.9)	96 (27.1)
Subjects completed all optional doses n (%)	1 (0.6)	4 (2.3)	5 (1.4)
Subject exposure (doses) [b]			
Mean (SD)	8.4 (2.06)	8.7 (1.76)	8.6 (1.92)
Median	9.0	9.0	9.0
Min, Max	1, 13	1, 13	1, 13
Number of doses n (%)			
1	4 (2.2)	2 (1.1)	6 (1.7)
2	3 (1.7)	1 (0.6)	4 (1.1)
3	2 (1.1)	4 (2.3)	6 (1.7)
4	3 (1.7)	0	3 (0.8)
5	7 (3.9)	3 (1.7)	10 (2.8)
6	2 (1.1)	3 (1.7)	5 (1.4)
7	10 (5.6)	9 (5.1)	19 (5.4)
8	13 (7.3)	22 (12.5)	35 (9.9)
9	100 (56.2)	100 (56.8)	200 (56.5)
10	25 (14.0)	22 (12.5)	47 (13.3)
11	7 (3.9)	5 (2.8)	12 (3.4)
12	1 (0.6)	2 (1.1)	3 (0.8)
13	1 (0.6)	3 (1.7)	4 (1.1)
Number of missed planned doses n (%)			
1	17 (9.6)	30 (17.0)	47 (13.3)
2	10 (5.6)	11 (6.3)	21 (5.9)
>2	15 (8.4)	7 (4.0)	22 (6.2)
Treatment compliance (%) [c]			
Mean	93.0	94.4	93.7
Median	100.0	100.0	100.0
SD	15.85	12.87	14.44
Min, Max	17, 100	13, 100	13, 100
Treatment compliance category n (%) [c]			
< 75%	19 (10.7)	9 (5.1)	28 (7.9)
>= 75%	159 (89.3)	167 (94.9)	326 (92.1)

Max=Maximum; Min=Minimum; SD=Standard deviation. n=number of subjects in the specified category with non-missing values; N=number of subjects in the treatment group analysis set. [a] Treatment duration is calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption. [b] Exposure to study medication is derived as the number of doses (both planned and optional) taken between the first dosing date and the last dosing date. [c] Treatment compliance is calculated as: (number of planned doses taken) / (number of planned doses) x100. The number of planned doses will be the doses from day 1 to the date of last study medication administration, as reported on the study CRF, excluding optional doses. Source: Table 14.1.5.1b and Listing 16.2.5b of MYL-1701P-3001, 52 Weeks CSR

Out of 96 subjects, 54 (30.3%) subjects in MYL-1701P arm and 42 (23.9%) subjects in Eylea arm received at least one additional optional dose of the study drug. Proportions of subjects receiving > 9 planned injections are discussed in Section *Results – Outcomes and estimation* (see *Other Secondary Efficacy Parameters*).

2.4.7.2. Adverse events

The provided safety database is considered sufficient to assess the comparability of common (≥1/100 to <1/10) and very common (≥1/10) adverse events. However, it is too small to inform on less frequently occurring adverse events. This approach is considered adequate for biosimilar development.

TEAEs overall

For an overall summary of AE see Table 25. TEAE leading to discontinuation are summarized in detail in Table 42. The overall incidence of TEAE was comparable between the study arms. More subjects experienced at least one related TEAE in the Eylea arm [12/176 (6.8%)] compared to MYL-1701P [5/178 (2.8%)]. Similarly, 3/176 (1.7%) experienced a related serious TEAE in the Eylea arm compared to zero in the MYL-1701P group. Yet, the majority of TEAEs were mild or moderate in severity.

Overall, 6 subjects experienced TEAEs leading to death during the study; 2 (1.1%) subjects in the MYL-1701P arm and 4 (2.3%) subjects in the Eylea arm. All deaths occurring during the study are described in detail and discussed in Section *2.4.7.3*.

Table 25: Overall Summary of Adverse Events – Safety Set

AE Category	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any AE	142 (79.8)	551	141 (80.1)	548	283 (79.9)	1099
Any TEAE	138 (77.5)	508	138 (78.4)	503	276 (78.0)	1011
Any Related TEAE	5 (2.8)	16	12 (6.8)	29	17 (4.8)	45
Any Serious TEAE	31 (17.4)	44	23 (13.1)	34	54 (15.3)	78
Any Related Serious TEAE	0	0	3 (1.7)	4	3 (0.8)	4
Any TEAE Leading to Death	2 (1.1)	3	4 (2.3)	4	6 (1.7)	7
Any Injection Procedure Related TEAEs	26 (14.6)	42	20 (11.4)	43	46 (13.0)	85
Any TEAE Leading to Discontinuation of Study Drug	3 (1.7)	3	3 (1.7)	4	6 (1.7)	7
TEAEs by Maximum Severity [a]						
Mild	59 (33.1)	151	61 (34.7)	166	120 (33.9)	317
Moderate	64 (36.0)	118	59 (33.5)	111	123 (34.7)	229
Severe	13 (7.3)	19	12 (6.8)	15	25 (7.1)	34
Life-Threatening	0	0	2 (1.1)	2	2 (0.6)	2
Death	2 (1.1)	3	4 (2.3)	4	6 (1.7)	7

AE = Adverse Events; SAE = Serious Adverse Events; TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set. Note: Classifications of AEs are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. An AE is defined as a TEAE if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET.
[a] For subjects with multiple events of various severities or relationships, only the event with the highest severity or strongest relationship is counted. Source: Table 14.3.1.1.1b and Listing 16.2.7.1b

A summary of **non-ocular TEAEs** by SOC and PT that were reported for ≥2% of the subjects by PT in either arm is provided in Table 26.

Non-ocular TEAEs were overall comparable between the treatment groups. However, more subjects treated with MYL-1701P reported SOC infections and infestations [55/178 (30.9%)] compared to subjects in the Eylea group [41/176 (23.3%)]. The following corresponding PTs were reported in higher incidence in MYL-1701P arm than in Eylea arm: nasopharyngitis (7.9% vs 5.7%), sinusitis (2.2% vs 1.1%), bronchitis, influenza and pneumonia (in each 2.2% vs 0.6%), respiratory tract infection (1.1% vs 0%). In addition, PTs pyrexia was reported in 3.9% in MYL-1701P arm compared to 1.7% in Eylea arm and cough was reported in 3.4% (MYL-1701P) vs 0.6% (Eylea), which could indicate the higher incidence in the risk of (especially respiratory tract) infections. No ADRs related to the respiratory system are stated in section 4.8 of provided SmPC or in SmPC of Eylea. Upon request, the Applicant provided more details on the occurrence of higher incidence of reported infections in the MYL-1701P arm. All reported events were assessed as not related. Most events were mild or moderate in severity. Only 2 events (2.8%) were severe (1 in MYL-1701P arm and 1 in Eylea arm), and 2 (2.8%) were fatal (both in Eylea arm). A severe case in the MYL-1701P arm was PT Covid-19 pneumonia (also assessed as not related to a study drug).

Additionally, more subjects treated with MYL-1701P reported TEAE peripheral swelling assigned to the SOC General disorders & administration site conditions (2.8%) compared to subjects in the Eylea arm (0%). Upon request, more details were provided. Four (4) of them had swelling in lower extremities and 1 subject reported swelling of upper extremity. All the observed events were considered not related to a study drug by investigators. The severity was mild to moderate. No pattern in time to onset could be identified.

Finally, more subjects treated with MYL-1701P reported TEAEs of fall assigned to the SOC Injury, poisoning and procedural complications (3.9%) compared to subjects in the Eylea arm (0.6%). Upon request, more details were provided. All events were considered not related to IP by the investigator.

None of these events led to any interruption in the treatment schedule or drug discontinuation. All the events (falls) were resolved on the same day of onset. The severity was mild (4x) or moderate (3x). Two (2) subjects in MYL-1701P arm had a history of similar events. Applicant stated that visual acuity was maintained at the time of the fall indicating that the fall was not due to low vision.

Overall, the imbalance in non-ocular TEAEs observed between the treatment arms was not considered to impact the conclusion on similar safety, as those were mostly mild to moderate in severity, not related to study drug and concerned few patients.

Apart from those, the most frequently reported non-ocular TEAEs by PT were hypertension reported by 36 (10.2%) subjects (16 [9.0%] in MYL-1701P and 20 [11.4%] in Eylea arm); urinary tract infection reported by 15 (4.2%) subjects (7 [3.9%] in MYL-17101P arm and 8 [4.5%] in the Eylea arm).

Those events were reported in both groups at similar frequencies and no further concerns arise from these findings.

Table 26: Non-Ocular TEAEs by SOC and PT (≥2% of the subjects by PT) – Safety Set

System Organ Class [a] Preferred Term [a]	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any TEAE	116 (65.2)	389	115 (65.3)	342	231 (65.3)	731
Infections and infestations	55 (30.9)	95	41 (23.3)	60	96 (27.1)	155
Nasopharyngitis	14 (7.9)	19	10 (5.7)	10	24 (6.8)	29
Urinary tract infection	7 (3.9)	7	8 (4.5)	13	15 (4.2)	20
Upper respiratory tract infection	4 (2.2)	4	5 (2.8)	7	9 (2.5)	11
COVID-19	5 (2.8)	5	2 (1.1)	2	7 (2.0)	7
COVID-19 pneumonia	3 (1.7)	3	4 (2.3)	4	7 (2.0)	7
Sinusitis	4 (2.2)	4	2 (1.1)	2	6 (1.7)	6
Bronchitis	4 (2.2)	4	1 (0.6)	1	5 (1.4)	5
Influenza	4 (2.2)	4	1 (0.6)	1	5 (1.4)	5
Pneumonia	4 (2.2)	4	1 (0.6)	1	5 (1.4)	5
Investigations	29 (16.3)	46	21 (11.9)	44	50 (14.1)	90
Blood pressure increased	5 (2.8)	5	3 (1.7)	5	8 (2.3)	10
Blood glucose increased	4 (2.2)	4	2 (1.1)	2	6 (1.7)	6
Electrocardiogram abnormal	4 (2.2)	4	1 (0.6)	1	5 (1.4)	5
Metabolism and nutrition disorders	23 (12.9)	29	18 (10.2)	24	41 (11.6)	53
Diabetes mellitus	2 (1.1)	3	9 (5.1)	10	11 (3.1)	13
Hyperglycaemia	5 (2.8)	6	1 (0.6)	1	6 (1.7)	7
Vascular disorders	18 (10.1)	22	23 (13.1)	26	41 (11.6)	48
Hypertension	16 (9.0)	20	20 (11.4)	23	36 (10.2)	43
Gastrointestinal disorders	23 (12.9)	40	17 (9.7)	26	40 (11.3)	66
Diarrhoea	5 (2.8)	6	2 (1.1)	2	7 (2.0)	8
Nausea	3 (1.7)	3	4 (2.3)	5	7 (2.0)	8
Nervous system disorders	15 (8.4)	16	20 (11.4)	26	35 (9.9)	42
Headache	4 (2.2)	4	4 (2.3)	4	8 (2.3)	8
Diabetic neuropathy	4 (2.2)	4	3 (1.7)	3	7 (2.0)	7
Renal and urinary disorders	16 (9.0)	22	14 (8.0)	17	30 (8.5)	39
Chronic kidney disease	1 (0.6)	1	6 (3.4)	7	7 (2.0)	8
Musculoskeletal & connective tissue disorders	14 (7.9)	16	16 (9.1)	22	30 (8.5)	38
Back pain	6 (3.4)	6	5 (2.8)	5	11 (3.1)	11
Arthralgia	0	0	6 (3.4)	6	6 (1.7)	6
General disorders & administration site conditions	18 (10.1)	20	11 (6.3)	11	29 (8.2)	31
Pyrexia	7 (3.9)	7	3 (1.7)	3	10 (2.8)	10
Peripheral swelling	5 (2.8)	5	0	0	5 (1.4)	5
Injury, poisoning and procedural complications	15 (8.4)	20	10 (5.7)	19	25 (7.1)	39
Fall	7 (3.9)	7	1 (0.6)	1	8 (2.3)	8
Respiratory, thoracic and mediastinal disorders	10 (5.6)	13	6 (3.4)	7	16 (4.5)	20
Cough	6 (3.4)	6	1 (0.6)	1	7 (2.0)	7
Blood and lymphatic system disorders	3 (1.7)	3	6 (3.4)	8	9 (2.5)	11
Anaemia	0	0	4 (2.3)	4	4 (1.1)	4

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set. Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. [a] Totals for the number of subjects at SOC level are not necessarily the sum of those at the PT levels since a subject may report two or more different adverse events within the SOC level category. An AE is defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL 1701P or Eylea after randomization through EOS/ET. Source: Table 14.3.1.2b and Listing 16.2.7.1b

A summary of **ocular TEAEs** by SOC and PT that were reported for ≥2% of the subjects by PT in either arm is provided in Table 27.

Overall, the most frequently reported ocular TEAEs by PT were cataract, reported by 17 (4.8%) subjects (11 [6.2%] in MYL-1701P arm and 6 [3.4%] in Eylea arm); conjunctival haemorrhage, reported by 13 (3.7%) subjects (6 [3.4%] in MYL-1701P and 7 [4.0%] in Eylea arm); and IOP increased reported by 9 (2.5%) subjects (4 [2.2%] in MYL-1701P and 5 [2.8%] in Eylea arm). Hence, the eye disorder cataract was reported more frequently in the MYL-1701P arm, but the higher reported incidence of medical history of cataract in MYL-1701P arm (42.5% vs 35.8%) could have an impact on the observed higher incidence during the study. In contrast, other ocular TEAEs by PT were more frequently observed in the Eylea arm. The observed ocular TEAEs are listed ADR in the Eylea SmPC

and therefore within the expected safety profile of Eylea and overall comparable between treatment arms.

Table 27: Ocular TEAEs in Study Eye by SOC and PT (≥2% of the subjects by PT) – Safety Set

System Organ Class [a] Preferred Term [a]	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Ocular TEAE – Study Eye	55 (30.9)	88	52 (29.5)	109	107 (30.2)	197
Eye disorders	47 (26.4)	68	46 (26.1)	90	93 (26.3)	158
Cataract	11 (6.2)	11	6 (3.4)	6	17 (4.8)	17
Conjunctival haemorrhage	6 (3.4)	8	7 (4.0)	9	13 (3.7)	17
Eye pain	2 (1.1)	2	6 (3.4)	9	8 (2.3)	11
Vitreous floaters	4 (2.2)	4	4 (2.3)	4	8 (2.3)	8
Vitreous detachment	3 (1.7)	3	4 (2.3)	5	7 (2.0)	8
Retinal exudates	2 (1.1)	2	4 (2.3)	4	6 (1.7)	6
Investigations	5 (2.8)	10	5 (2.8)	15	10 (2.8)	25
Intraocular pressure increased	4 (2.2)	9	5 (2.8)	14	9 (2.5)	23

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number o subjects in the row category/N within the column category.
[a] Totals for the number of subjects at SOC level are not necessarily the sum of those at the PT levels since a subjec may report two or more different adverse events within the SOC level category.
An AE is defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET
Source: Table 14.3.1.2b and Listing 16.2.7.1b

A tabular summary of **intensity/severity of TEAEs** in both the treatment arms for safety population is provided in Table 28.

The severity of non-ocular and ocular TEAEs was comparable between treatment arms. The majority of ocular TEAEs were mild [in 80/354 (22.6%) of subjects in the study eye] to moderate [in 23/354 (6.5%) of subjects in the study eye]. In the study eye, severe ocular TEAEs were reported in one (0.6%) subject (PT: posterior capsule opacification) in the MYL-1701P arm and 3 (1.7%) subjects (PTs: macular hole, and vitreous detachment, vitreous detachment, cataract) in the Eylea arm. No ocular life-threatening ocular TEAEs were reported.

There were no subjects in the MYL-1701P arm and 2 (1.1%) subjects in the Eylea arm who reported life threatening event and 2 (1.1%) subjects in MYL-1701P arm and 4 (2.3%) subjects in Eylea arm died. All deaths occurring during the study are described in detail and discussed in Section *2.4.7.3*.

Table 28: TEAEs by Maximum Reported Intensity – Safety Set

AE Category	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any Ocular TEAEs by Maximum Severity [a]						
Study Eye						
Mild	43 (24.2)	56	37 (21.0)	79	80 (22.6)	135
Moderate	11 (6.2)	14	12 (6.8)	14	23 (6.5)	28
Severe	1 (0.6)	1	3 (1.7)	4	4 (1.1)	5
Life-Threatening	0	0	0	0	0	0
Death	0	0	0	0	0	0
Fellow Eye						
Mild	29 (16.3)	33	33 (18.8)	55	62 (17.5)	88
Moderate	10 (5.6)	10	15 (8.5)	17	25 (7.1)	27
Severe	0	0	1 (0.6)	1	1 (0.3)	1
Life-Threatening	0	0	0	0	0	0
Death	0	0	0	0	0	0
Any Non-ocular TEAEs by Maximum Severity [a]						
Mild	53 (29.8)	120	53 (30.1)	105	106 (29.9)	225
Moderate	49 (27.5)	96	46 (26.1)	87	95 (26.8)	183
Severe	12 (6.7)	18	10 (5.7)	11	22 (6.2)	29
Life-Threatening	0	0	2 (1.1)	2	2 (0.6)	2
Death	2 (1.1)	3	4 (2.3)	4	6 (1.7)	7

AE = Adverse Events; SAE = Serious Adverse Events; TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set. Note: Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. An AE is defined as a TEAE if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET. [a] For subjects with multiple events of various severities or relationships, only the event with the highest severity or strongest relationship is counted.
Source: Table 14.3.1.1.1b and Listing 16.2.7.1b

A summary of the **TEAEs by relationship** with the study drugs is provided in Table 30. Upon request, details on the method of assessment of the causal relationship with the study drug were provided by the Applicant (Table 29).

Table 29: Details of Method of Assessment of the Causal Relationship with Study Drugs (Category, Causality, and Description)

Category	Causality	Description
DEFINITE	Causal relationship is certain	For example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLE	High degree of certainty for causal relationship	For example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
POSSIBLE	Causal relationship is uncertain	For example: the temporal relationship between study treatment exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal; could also be explained by disease or other drugs.
UNLIKELY	Causal relationship is improbable	Another explanation is more likely such as disease, environment, or other medication. Does not represent a known reaction to study drug.
UNRELATED / NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible

The majority of TEAEs were considered not related [in 231/354 (65.3%) of subjects] or unlikely [28/354 (7.9%) of subjects] related to study drug and there were no notable differences in frequencies between the treatment arms. All the definitely related TEAEs were ocular TEAEs in study eye. Most of those are known undesirable effects of Eylea (SmPC), except papilledema, which occurred in the MYL-1701P treatment arm. This was a single AE of moderate severity, which occurred eight days after the first dose of MYL-1701P. The event of papilledema resolved following treatment with cetirizine, topical dexamethasone and topical nepafenac. The patient did not receive any further doses of study drug and was withdrawn from the study. Since this was an isolated event, no concern regarding a similar safety profile of Eylea and MYL-1701P is raised.

Non-ocular TEAEs that were possibly related to the study drugs were cardiac arrest, embolic stroke (one subject) and brain stem infarction (one subject) in the Eylea arm. Those events are Adverse Events of Interest and are discussed in the next section.

Table 30: TEAEs by Maximum Relationship to Study Drug – Safety Set

AE Category	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
TEAEs by Maximum Relationship to Investigational Drug [a]						
Not related	121 (68.0)	447	110 (62.5)	333	231 (65.3)	780
Unlikely	12 (6.7)	17	16 (9.1)	32	28 (7.9)	49
Possible	1 (0.6)	1	8 (4.5)	12	9 (2.5)	13
Probable	2 (1.1)	2	1 (0.6)	1	3 (0.8)	3
Definite	2 (1.1)	13	3 (1.7)	15	5 (1.4)	28

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set.
Note: Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on numbe of subjects in the row category/N within the column category. An AE is defined as a TEAE if the first onset (o worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea afte randomization through EOS/ET. [a] For subjects with multiple events of various severities or relationships, only th event with the highest severity or strongest relationship is counted. Source: Table 14.3.1.1.1b and Listing 16.2.7.1b

A summary of the **drug related TEAEs** by SOC and PT (≥2 Subjects by PT) is provided in the Table 31.

The frequency of drug related TEAEs (≥ 2 subjects by PT) was higher in Eylea treated subjects [12/176 (6.8%)] compared to the MYL-1701P arm [5/178 (2.8%)]. Those events are known undesirable effects of Eylea (SmPC), and appear to be less common in the MYL-1701P arm.

Table 31: Summary of Drug Related TEAEs by SOC and PT (≥2 Subjects by PT) – Safety Set

	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
System Organ Class [a] Preferred Term [a]	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any TEAE	5 (2.8)	16	12 (6.8)	29	17 (4.8)	45
Eye disorders	4 (2.2)	7	9 (5.1)	16	13 (3.7)	23
Vitreous floaters	1 (0.6)	1	2 (1.1)	2	3 (0.8)	3
Investigations	2 (1.1)	7	3 (1.7)	10	5 (1.4)	17
Intraocular pressure increased	1 (0.6)	6	3 (1.7)	10	4 (1.1)	16

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set. Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. [a] Totals for the number of subjects at SOC level are not necessarily the sum of those at the PT levels since a subject may report two or more different adverse events within the SOC level category. Drug Related TEAEs includes TEAEs with relationship of definite, probable and possible to study drug. An AE is defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET. Source: Table 14.3.1.10b and Listing 16.2.7.1b

In conclusion, the overall safety profile appears acceptable and comparable in both treatment arms.

Adverse Events of Interest

Major adverse **cardiovascular events** (MACE) have been reported as adverse events of interest, since there is a theoretical risk of cardiovascular effects upon systemic anti-VEGF treatment. The

masked independent MACE adjudication committee reviewed potential cardiovascular events occurring in the MYL-1701P-3001 study. A total of 45 TEAEs required full committee adjudication. Of those, nine events (Table 32) were classified as MACE and occurred in seven subjects (2 (1.1%) subjects in MYL-1701P arm vs 5 (2.8%) subjects in Eylea arm). Hence, more MACE occurred in the Eylea arm. Of those, each one event of cardiac arrest, embolic stroke (one subject) and brain stem infarction (one subject) in the Eylea arm were classified possibly related to the study drug. Although cardiac arrest and embolic stroke in one subject were considered non-fatal, the subject died after withdrawal from study.

The higher frequency of MACE in the Eylea group may suggest higher systemic aflibercept concentrations, which may impact the conclusion on biosimilarity between MYL-1701P and Eylea. In the PK subset, the maximum concentration of systemic aflibercept was indeed considerably higher in the Eylea arm (244.30 ng/ml) compared to MYL-1701P (108.40 ng/ml). The observed maximum concentration of systemic Eylea (244.30 ng/ml) was measured at V2 in a single patient (no MACE observed), and decreased to 15.47 ng/ml by V7A, which was below the overall mean concentration at that time point (Listing 16.2.9.5b), and is therefore of no concern. Of the patients experiencing a MACE, one subject was included in the PK subset, and had a maximum Eylea concentration of 69.95 ng/ml at V2, which decreased below the limit of detection at V7. Hence, elevated systemic aflibercept concentrations do not appear to be a safety concern regarding MACE.

Table 32: Summary of Adverse Events Categorised as MACE Events

SI	Treatment Arm	Preferred Term	Type of MACE Event
1	MYL-1701P	Thrombotic cerebral infarction	Stroke (non-fatal)
2	Eylea	Myocardial infarction	Myocardial infarction (non-fatal)
3	Eylea	Cardiac arrest	Myocardial infarction (non-fatal)
4	Eylea	Death	Cardiovascular death
5	Eylea	Embolic stroke	Stroke (non-fatal)
6	Eylea	Brain stem infarction	Stroke (non-fatal)
7	Eylea	Embolic cerebral infarction	Stroke (non-fatal)
8	Eylea	Myocardial infarction	Cardiovascular death
9	MYL-1701P	Death	Cardiovascular death

MACE = Major adverse cardiovascular event. Note: Classifications of adverse events are based on the MedDRA (version 24.1). Source: Listing 16.2.7.4b

A summary of **ocular injection procedure related TEAEs** by SOC and PT (≥2% of the subjects by PT) is provided in Table 33.

Although a higher incidence of any ocular injection procedure related TEAEs was observed in the MYL-1701P arm (14.6% vs 11.4%), reported TEAEs (≥2% of the subjects by PT) do not show any differences in comparison to the Eylea arm and were in line with known undesirable effects of Eylea (SmPC). Thus, the safety regarding the ocular injection TEAEs is considered to be similar between both treatment arms.

Table 33: Ocular Injection Procedure Related TEAE by SOC and PT (≥2 % of the subjects by PT) – Safety Set

System Organ Class [a] Preferred Term [a]	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any TEAE	26 (14.6)	42	20 (11.4)	43	46 (13.0)	85
Any Ocular TEAE	26 (14.6)	42	20 (11.4)	42	46 (13.0)	84
Eye disorders	19 (10.7)	25	18 (10.2)	29	37 (10.5)	54
Conjunctival haemorrhage	6 (3.4)	8	6 (3.4)	8	12 (3.4)	16
Vitreous floaters	4 (2.2)	4	3 (1.7)	3	7 (2.0)	7
Eye pain	2 (1.1)	2	4 (2.3)	5	6 (1.7)	7
Investigations	5 (2.8)	10	3 (1.7)	12	8 (2.3)	22
Intraocular pressure increased	4 (2.2)	9	3 (1.7)	12	7 (2.0)	21

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set. Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. [a] Totals for the number of subjects at SOC level are not necessarily the sum of those at the PT levels since a subject may report two or more different adverse events within the SOC level category. An AE is defined as a TEAE if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET.
Source: Table 14.3.1.7b and Listing 16.2.7.1b

One event related to **ocular inflammation** was reported by one subject from Eylea arm ("eye inflammation"). The event was a mild (Grade-1) non-serious adverse event assessed by the Principal Investigator as possibly related to the study drug and the treatment was temporarily interrupted because of this event. The event resolved after 51 days. This subject did not test positive for ADA during any of the study visits. There were no events of endophthalmitis reported in the study.

2.4.7.3. Serious adverse event/deaths/other significant events

Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
- Is an important medical event.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

Serious TEAEs

An overview of serious TEAEs reported for ≥1% subjects by PT in either treatment arm is presented in Table 34.

Overall, there were more subjects with serious TEAE for MYL-1701P [31/178 (17.4%)] compared to Eylea [23/176 (13.1%)]. Numerically the highest difference was reported for PT infections and infestations. Similar to overall non-ocular TEAEs and as discussed above, as these events had different origins, no single type of infection could be identified. Hence, the overall higher incidence of PT infections and infestations in the MYL-1701P group (7.3% vs 3.4% in the Eylea group) may be a chance finding. Similarly, as most serious TEAE were reported in both groups and at low numbers per PT it is difficult to draw any final conclusions. With the available data, the overall safety profile seems acceptable and comparable in both treatment arms.

Table 34: Serious TEAEs by SOC and PT (≥1% of the subjects by PT) – Safety Set

System Organ Class [a] Preferred Term [a]	MYL-1701P (N=178)		Eylea (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any Serious TEAE	31 (17.4)	44	23 (13.1)	34	54 (15.3)	78
Infections and infestations	13 (7.3)	13	6 (3.4)	6	19 (5.4)	19
COVID-19 pneumonia	3 (1.7)	3	4 (2.3)	4	7 (2.0)	7
Pneumonia	2 (1.1)	2	1 (0.6)	1	3 (0.8)	3
COVID-19	2 (1.1)	2	0	0	2 (0.6)	2
Cardiac disorders	4 (2.2)	4	6 (3.4)	7	10 (2.8)	11
Cardiac failure	2 (1.1)	2	0	0	2 (0.6)	2
Myocardial infarction	0	0	2 (1.1)	2	2 (0.6)	2
Injury, poisoning and procedural complications	3 (1.7)	3	1 (0.6)	1	4 (1.1)	4
Femoral neck fracture	2 (1.1)	2	0	0	2 (0.6)	2
Skin and subcutaneous tissue disorders	2 (1.1)	2	1 (0.6)	2	3 (0.8)	4
Diabetic foot	2 (1.1)	2	1 (0.6)	2	3 (0.8)	4

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set. Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. [a] Totals for the number of subjects at SOC level are not necessarily the sum of those at the PT levels since a subject may report two or more different adverse events within the SOC level category. An AE is defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET. Source: Table 14.3.1.5b and Listing 16.2.7.1b

There were 3 (0.8%) serious **ocular TEAE** in the study eye reported in 3 subjects: 1 (0.6%) subject in the MYL-1701P arm and 2 (1.1%) subjects in the Eylea arm. The events were one incidence of 'eye haemorrhage' in the MYL-1701P and one incidence of 'corneal oedema' and one incidence of 'vitreous detachment' in the Eylea arm, which was considered not related to the study drug by the Investigator (Table 35). It remains unclear whether the other reported serious ocular TEAEs were considered related or not related to the study drug. Regardless, these events are known undesirable effects of Eylea and the frequency in both study arms is comparable. No serious ocular TEAE was reported in the fellow eye.

Table 35: Summary of treatment-emergent SAEs by System Organ Class and Preferred Term Safety Analysis Set

Category - Ocular Serious TEAEs Study Eye

System Organ Class [a] Preferred Term [a]	MYL-1701P (N=178)		Eylea® (N=176)		Overall (N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any Serious TEAE	1 (0.6)	1	2 (1.1)	2	3 (0.8)	3
Eye disorders	1 (0.6)	1	2 (1.1)	2	3 (0.8)	3
Corneal oedema	0	0	1 (0.6)	1	1 (0.3)	1
Eye haemorrhage	1 (0.6)	1	0	0	1 (0.3)	1
Vitreous detachment	0	0	1 (0.6)	1	1 (0.3)	1

Deaths

Overall, 6 subjects experienced TEAEs leading to death during the study; two in MYL-1701P arm and four in Eylea arm. Narratives for all patients have been provided by the Applicant.

In MYL-1701P arm, one subject reported serious TEAEs acute coronary syndrome (not related) and Covid-19 infection (not related) which led to death; one subject died due to unknown cause (not related). In the Eylea arm, one subject died due to pneumonia (not related); one subject died due to myocardial infarction (not related); one subject died due to COVID-19 pneumonia (not related). One death in Eylea arm the cause of which was unknown as no autopsy was done. The subject was withdrawn from the study earlier because of other Grade 4 SAEs, embolic stroke (possibly related) and cardiac arrest (possibly related). The event 'death' (not related) was reported after the protocol specified safety follow-up period had elapsed post ET visit.

All the events leading to death were considered not related to the study drug by the Investigator, which can be followed. All patients had prior/concomitant co-morbidities and two subjects died from COVID19 infections. No concerns regarding aflibercept treatment arise from these fatal events.

2.4.7.4. Laboratory findings

No trends towards significant increase or significant decrease in mean values over time were seen for any of the laboratory parameters (**hematology and serum chemistry**) in either treatment arm.

Mean **HbA1c** was generally stable across the study in both study arms. Few subjects who had 'normal' (values less than 6.5%) HbA1c at baseline shifted to 'high' values (values ≥ 6.5%) at Week 52 in both arms (4.6% in MYL-1701P arm compared to 6.1% in Eylea arm).

There were no specific trends towards abnormal values of **urinalysis** parameters in either study arms.

There were no **pregnancies** reported during the study.

There were minimal changes in **vital signs** parameters [pulse (beats/min), body temperature (ºC), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg)] across study with no differences or trends observed between the two study arms.

No clinically meaningful trends were noted between baseline and Week 52 for any of the recorded **ECG** parameters [including QT, QTc (Fridericia's), heart rate (HR), QRS duration, PR and RR interval] between the study arms.

A summary of the ECG interpretation has been provided in Table 36. Abnormal ECG interpretation was observed more frequently in the MYL-1701P arm throughout the study duration, but was considered not clinically significant (NCS) in the majority of subjects. Furthermore, the proportion of subjects with ECG NCS abnormal was below the proportion at baseline from Week 24 onward. Clinically significant abnormal ECG was observed in similar proportions of subjects between the study arms throughout the study duration.

Table 36: Summary of ECG Interpretation Safety Analysis Set

Visit ECG Interpretation	MYL-1701P (N=178) n (%)	Eylea® (N=176) n (%)
Screening		
Normal	86 (48.3)	93 (52.8)
Abnormal NCS	84 (47.2)	77 (43.8)
Abnormal CS	7 (3.9)	6 (3.4)
Not Done	0	0
Visit 1 (Baseline)		
Normal	80 (44.9)	97 (55.1)
Abnormal NCS	93 (52.2)	75 (42.6)
Abnormal CS	5 (2.8)	4 (2.3)
Not Done	0	0
Visit 3 (Week 1)		
Normal	77 (43.3)	88 (50.0)
Abnormal NCS	90 (50.6)	75 (42.6)
Abnormal CS	6 (3.4)	7 (4.0)
Not Done	0	0
Visit 9 (Week 24)		
Normal	69 (38.8)	87 (49.4)
Abnormal NCS	77 (43.3)	59 (33.5)
Abnormal CS	4 (2.2)	5 (2.8)
Not Done	1 (0.6)	0
Visit 16 (Week 52)		
Normal	77 (43.3)	88 (50.0)
Abnormal NCS	79 (44.4)	64 (36.4)
Abnormal CS	3 (1.7)	2 (1.1)
Not Done	0	1 (0.6)
Visit 16 (EOT/EOS)		
Normal	79 (44.4)	89 (50.6)
Abnormal NCS	81 (45.5)	66 (37.5)
Abnormal CS	3 (1.7)	2 (1.1)
Not Done	0	1 (0.6)

NCS = Not clinically significant; CS = Clinically significant
n=number of subjects in the specified category with non-missing values; N=number of subjects in the treatment group analysis set.

Ophthalmological Examinations

Ophthalmological examination included intraocular pressure (IOP), indirect ophthalmoscopy, and slit lamp biomicroscopy. All analyses were performed for the study eye as well as for the fellow eye.

IOP was measured from baseline through Week 52 (Visit 16), and at each visit twice (pre-dose, post-dose) whenever a dose was administered (see Table 37). Pre- and post-dose mean values as well as mean differences pre- and post-dose were similar between study arms.

There were 9 events of increased IOP experienced by 4 (2.2%) subjects in MYL-1701P arm as compared to 12 events experienced by 3 (1.7%) subjects in the Eylea arm (Table 40, Section *2.4.7.2. Adverse Events*). Other than these, there were no significant differences in mean post-dose IOP values between the two treatment arms. IOP is a known common (≥1/100 to <1/10) undesirable effect of Eylea, and hence the incidence in both study arms was in line with the expected safety profile.

Table 37: Summary of Intraocular Pressure (mmHg) in Study Eye – Safety Set

Visit	Status		MYL-1701P (N=178)		Eylea (N=176)	
			Observed value	Change from Baseline	Observed value	Change from Baseline
Visit 1 (Baseline)	Pre-dose	Mean (SD)	15.4 (2.86)		15.4 (2.97)	
	Post-dose		17.2 (3.55)	1.8 (3.33)	17.6 (3.94)	2.1 (3.80)
	Post-dose minus Pre-dose		1.8 (3.33)		2.1 (3.80)	
Visit 9 (Week 24)	Pre-dose		15.0 (2.90)	-0.04 (3.07)	15.0 (2.86)	-0.05 (3.14)
	Post-dose		17.4 (3.31)	2.1 (3.66)	17.5 (3.59)	2.0 (3.87)
	Post-dose minus Pre-dose		2.5 (3.09)		2.5 (3.93)	
Visit 15 (Week 48)	Pre-dose		15.5 (2.90)	0.3 (3.10)	15.5 (2.99)	-0.3 (2.91)
	Post-dose		17.9 (3.57)	2.7 (4.05)	17.4 (3.77)	2.1 (3.70)
	Post-dose minus Pre-dose		2.4 (3.62)		2.4 (3.50)	
Visit 16 (Week 52)	Pre-dose		15.5 (2.85)	0.3 (3.29)	15.4 (2.91)	-0.0 (2.83)
Visit 16 (EoT/EOS)	Pre-dose		15.6 (2.87)	0.3 (3.27)	15.4 (2.91)	-0.0 (2.80)

Source: Table 14.3.7.1b and Listing 16.2.6.3b

All clinically significant abnormal findings of **indirect ophthalmoscopy** and **slit-lamp biomicroscopy** examination during the study were reported as AEs, which is considered appropriate.

2.4.7.5. Immunological events

ADA assessment approach

The Applicant has adopted a three-tiered ECL-based set of bridging assay format to screen, confirm and quantify aflibercept specific antibodies in human serum matrix. In brief, serum samples are acidified and neutralised before interacting with biotinylated- and sulfo-tagged - aflibercept. ECL measurement is performed with a Meso QuickPlex SQ 120 reader in duplicates on BSA blocked plates after addition of MSD Gold Read Buffer A. A polyclonal rabbit immune response spiked into pooled negative serum is used as positive control. All critical reagents, drugs, matrices and antibodies and used lot numbers were well described. The assay was validated for its precision, specificity, selectivity, cross-reactivity, and robustness. Intra- and inter-assay precision were both below 10%. Screening and confirmatory-assay sensitivities were 5 and 18ng/ml respectively. Cut points for the screening, confirmation and titer assay were estimated in 48 naïve pre-dose samples at respective error rates of 5, 1 and 1%. The negative control serum pool consisted of 80 healthy individuals and was spiked with a polyclonal rabbit antibody at three concentration levels of 23, 100 and 1000ng/ml to serve as positive control. Antigenic equivalence to US-Eylea was demonstrated, and the absence of a prozone effect was confirmed for antibody levels up to 50µg/ml. Benchtop and freeze-thaw sample stability, as well as drug tolerance up to 10µg/ml were confirmed. The assay was tolerant to haemolytic and lipemic samples and to VEGF levels up to 50ng/ml and. Taken together, the adopted three-tiered approach for determination of ADAs was well described and developed. It is considered state of the art and valid for its intended use.

Assessment of Neutralising antibodies

The Applicant presented a qualitative assay for detection of neutralising ADA's. In brief, acidified serum samples are incubated in microtiter plates with immobilised aflibercept, and simultaneously neutralised. Drug specific antibodies are eluted - again under acid conditions - after washing. The Applicant justified that induced drug specific antibodies retained their functionality after both acid treatment steps. They are transferred into a chemiluminescence plate, where they interact with sulfo-tagged aflibercept, with and without the competitor VEGF. Chemiluminescent detection is performed with a Meso QucikPlex SQ 120 reader in presence of MSD Gold Read buffer A. The presence of neutralizing antibody (NAb) against aflibercept is reflected by assay signal inhibition in the presence of

VEGF, the target ligand of aflibercept. Two cut points were determined: Run specific detection cut point (5% false-positive error rate) is defined as the minimum level of response required for a sample to be evaluated for NAb positivity using the Percent Inhibition Cut Point (1% false-positive error rate), which corresponds to level of signal reduction after addition of excess VEGF in solution, at and above which the sample is considered NAb positive. All critical reagents, drugs, matrices and antibodies including lot numbers were well described. The assay was validated for its precision, sensitivity, specificity, selectivity, cross-reactivity, and robustness. Intra- and inter-assay precision were both below 10%. Sensitivities for sample evaluation and confirmed positivity corresponded to 8 and 18 ng/ml, respectively. A serum pool of 20 non-reactive individuals served as negative control, and was spiked with a murine monoclonal anti-aflibercept antibody with neutralising potential at 20, 200 and 2000ng/ml as positive control. Cut points for evaluation and confirmed neutralising potential were estimated in 30 naïve pre-dose samples at respective error rates of 5 and 1%. Benchtop and freeze-thaw sample stability, and drug tolerance up to 10µg/ml were confirmed for MYL-1701P and Eylea. Specificity was demonstrated using an irrelevant antibody(anti-orentia) at 2µg/ml. The assay was tolerant to haemolytic or lipemic samples and to Avastin, Lucentis and VEGF levels up to 4000, 200 and 10ng/ml, respectively. The absence of a prozone effect was observed for antibody levels up to 50µg/ml, and bridging to a different lot of biotinylated aflibercept did not impact on the assay readout.

Taken together, presented assay for determination of neutralising properties was well described and established. It measures a reduction of binding to the target VEGF and thus reflects the mechanism of action of the drug which mediates its clinical effect. The assay is considered highly relevant, was setup correctly and fully validated. Thus, it is considered valid for its intended use.

Immunogenicity

The summary of incidence of ADA and NAb by Visit and by overall, in safety analysis set is provided in Table 38 and Table 39 (overall ADA and NAb incidence: sum of both treatment induced and treatment boosted ADA-positive patients as a proportion of the evaluable patient population).

At baseline, similar proportions of patients were positive for ADA: 17/178 (9.6%) of subjects in the MYL-1701P group compared to 18/176 (10.2%) in the Eylea group. One subject was positive for NAb (MYL-1701P group). The overall incidence of ADA positive subjects at baseline was higher compared to what was observed in registrational Eylea studies (VIVID/VISTA), which may be explained by different sensitivity and specificity of the assays used. Importantly, the incidence of ADA during the present study was similar between MYL-1701P and Eylea, supporting biosimilarity.

The overall proportion of ADA positive subjects remained similar throughout the study period ranging from 5.9% to 9.7% in the MYL-1701P arm at post-baseline visits compared to 8.7% to 10.6% in the Eylea arm. Some of these subjects had transient ADA positivity only in some visits with low titers. Overall, 2.8% subjects in MYL-1701P arm and 5.7% subjects in Eylea arm reported either treatment induced (developed any time after the initiation of drug administration in a subject without pre-existing ADA), or treatment boosted ADA (titer was at least 4 times the baseline titer in a subject who had a pre-existing ADA). Some of these subjects had positive ADA transiently at specific visits.

NAb positivity was mostly transient and present in specific visits in most cases. Overall, 2 subjects in MYL-1701P and 5 subjects in Eylea arm tested positive for NAb at least in one of the post-baseline visits. There were no subjects in MYL-1701P arm and 1 subject (0.6%) in Eylea arm among subjects having treatment boosted ADA that tested positive for NAb.

Mean titers were lower in the MYL-1701P treatment arm compared to Eylea at most time points, except at Week 1, when they were similar (17.902 [MYL-1701P] vs 15.745 [Eylea]). From Week 40, mean titers were more than 5-fold lower in the MYL-1701P group compared to Eylea, but SD was high in the Eylea group (e.g. at Week 52: Mean (SD) 18.324 (19.4393) [MYL-1701P] vs 135.906

(342.3518) [Eylea]). Upon request, it was confirmed by the Applicant that this result was driven by three subjects with exceptionally high ADA titers (>1:200) in the Eylea group. Reduced efficacy, as assessed by BCVA and CRT, was only observed in one subject particularly standing out (ADA titer >1:1000). Moreover, no correlation with the occurrence of NAb or TEAEs was observed.

Overall, immunogenicity appears lower in patients with MYL-1701P treatment compared to Eylea.

Table 38: Summary of ADA and Nab* Results by Visit and Treatment – Safety Set

Visit	Week	Parameter	MYL-1701P			Eylea		
			m	n	m/n (%)	m	n	m/n (%) (%)
Visit 1	Baseline	ADA	17	178	9.6	18	176	10.2
		NAb	1	178	0.6	0	176	0.0
Visit 3	Week 1	ADA	11	171	6.4	17	166	10.2
		NAb	0	171	0.0	0	166	0.0
Visit 4	Week 4	ADA	11	168	6.5	15	172	8.7
		NAb	0	168	0.0	0	172	0.0
Visit 5	Week 8	ADA	10	160	6.3	15	162	9.3
		NAb	0	160	0.0	1	162	0.6
Visit 7	Week 16	ADA	9	153	5.9	17	160	10.6
		NAb	1	153	0.7	3	160	1.9
Visit 9	Week 24	ADA	14	150	9.3	15	157	9.6
		NAb	0	150	0.0	3	157	1.9
Visit 11	Week 32	ADA	14	145	9.7	14	156	9.0
		NAb	1	145	0.7	2	156	1.3
Visit 13	Week 40	ADA	11	149	7.4	14	158	8.9
		NAb	0	149	0.0	2	158	1.3
Visit 16	Week 52	ADA	10	157	6.4	15	152	9.9
		NAb	1	157	0.6	2	152	1.3
Visit 16	EOT/EOS	ADA	10	161	6.2	15	155	9.7
		NAb	1	161	0.6	2	155	1.3

ADA = Anti-Drug antibodies; NAb = Neutralizing antibodies ADA incidence: m = Sum of both treatment induced, and treatment boosted ADA-positive patients; n = number of patients with evaluable ADA results; NAb incidence: n=number of patients with evaluable ADA results (baseline and at least one post-baseline); m=number of patients with positive NAb result. *NAb testing was done only when ADA were present.
Source: Table 14.4b and Listing 16.2.9.4b

Table 39: Incidence of Treatment Induced and Boosted ADA and Nab – Safety Set

Parameter	ADA Result	MYL-1701P n (%)	Eylea n (%)
Subjects (m)		177	176
ADA incidence	Total	5 (2.8)	10 (5.7)
	Treatment induced	5 (2.8)	8 (4.5)
	Treatment boosted	0	2 (1.1)
NAb incidence	Total	0	1 (0.6)
	Treatment induced	0	0
	Treatment boosted	0	1 (0.6)

ADA = Anti-Drug antibodies; NAb = Neutralizing antibodies. For ADA summary: m=number of patients with evaluable ADA results (baseline and at least one post-baseline assessment); n=number of patients with treatment induced ADA or treatment boosted ADA results. Source: Table 14.4b and Listing 16.2.9.4a

The mean change (SD) in BCVA from baseline up to Week 52 in ADA positive subjects was 11.25 (8.175) letters in MYL-1701P arm and 10.85 (5.998) letters in Eylea arm. Neither the BCVA change from baseline nor equivalence was compromised by the occurrence of ADA. In fact, at Week 8 the mean change from baseline in BCVA was even higher and very similar in both treatment arms in the ADA positive subgroup (Table in Section *Ancillary analyses*). No clinically relevant trends were observed in specific NAb positive subjects with respect to BCVA gain or CRT reduction over time during the study.

The incidences of overall TEAEs at Week 52 by ADA status in safety analysis set is provided in Table 40. Overall, no clinically relevant difference in the incidence of TEAEs observed between the study arms. Among the three subjects with a positive NAb result at some visit during the study in MYL-1701P arm, one subject reported an ocular TEAE (one subject; visual impairment). Among the 5 subjects with a positive NAb result in Eylea arm, two subjects had reported ocular TEAEs (one subject; diabetic retinal oedema [worsening] and one subject; retinal exudates).

Table 40: Incidence of overall TEAEs and Study Eye Ocular TEAEs at Week 52 by ADA Status – Safety Set

	MYL-1701P (N = 178)		Eylea (N = 176)	
AE Category	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
ADA positive				
Overall TEAEs	16 (9.0)	62	18 (10.2)	61
Study Eye Ocular TEAEs	6 (3.4)	16	8 (4.5)	14
ADA negative				
Overall TEAEs	122 (68.5)	446	120 (68.2)	442
Study Eye Ocular TEAEs	49 (27.5)	72	44 (25.0)	95

ADA = Anti-drug Antibody specific to treatment administered, TEAE = Treatment Emergent Adverse Events n=number of subjects in the specified category with non-missing values; N=number of subjects in the treatment group analysis set. Percentage %) based on number of subjects in the row category/N within the column category. Source: Table 14.3.1.1.2b; Listing 16.2.7.1b, 16.2.9.4b

A tabular summary of TEAEs by SOC and PT for ADA positive subjects (safety set) is provided in Table 41. There were no meaningful differences in the ocular TEAEs between the two treatment arms.

Table 41: Summary of Ocular TEAEs by SOC and PT for ADA Positive Subjects – Safety Set

System Organ Class [a] Preferred Term [a]	MYL-1701P (N=22)		Eylea (N=26		Overall (N=48)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any Ocular TEAEs Study Eye	6 (27.3)	16	8 (30.8)	14	14 (29.2)	30
Eye disorders	6 (27.3)	8	6 (23.1)	11	12 (25.0)	19
Eye pain	0	0	2 (7.7)	3	2 (4.2)	3
Retinal exudates	0	0	2 (7.7)	2	2 (4.2)	2
Conjunctival haemorrhage	1 (4.5)	3	0	0	1 (2.1)	3
Eye irritation	0	0	1 (3.8)	2	1 (2.1)	2
Foreign body sensation in eyes	0	0	1 (3.8)	2	1 (2.1)	2
Cataract	1 (4.5)	1	0	0	1 (2.1)	1
Conjunctival disorder	0	0	1 (3.8)	1	1 (2.1)	1
Eye pruritus	1 (4.5)	1	0	0	1 (2.1)	1
Ocular discomfort	0	0	1 (3.8)	1	1 (2.1)	1
Visual impairment	1 (4.5)	1	0	0	1 (2.1)	1
Vitreal cells	1 (4.5)	1	0	0	1 (2.1)	1
Vitreous floaters	1 (4.5)	1	0	0	1 (2.1)	1
Investigations	1 (4.5)	6	2 (7.7)	2	3 (6.3)	8
Intraocular pressure increased	1 (4.5)	6	2 (7.7)	2	3 (6.3)	8
General disorders & administration site conditions	1 (4.5)	1	0	0	1 (2.1)	1
Injection site pain	1 (4.5)	1	0	0	1 (2.1)	1
Infections and infestations	0	0	1 (3.8)	1	1 (2.1)	1
Conjunctivitis	0	0	1 (3.8)	1	1 (2.1)	1
Injury, poisoning and procedural complications	1 (4.5)	1	0	0	1 (2.1)	1
Corneal abrasion	1 (4.5)	1	0	0	1 (2.1)	1

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set for ADA positive subjects. Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. [a] Totals for the number of subjects at SOC level are not necessarily the sum of those at the PT levels since a subject may report two or more different adverse events within the SOC level category. An AE is defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET.
Source: Table 14.3.1.11b and Listing 16.2.7.1b, 16.2.9.4b.

A secondary objective of study MYL-1701P-3001 was to compare the impact of immunogenicity on safety. Upon request, the Applicant provided the safety analysis comparing treatment-induced and treatment-boosted ADA/NAb positive subjects and ADA/NAb negative subjects, which did not provide any comprehensive findings.

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

Not applicable for biosimilars.

2.4.7.7. Discontinuation due to adverse events

Reasons for discontinuation are also described in Section *Results – Participant flow* (Table 3).

Overall, 36 (10.1%) subjects discontinued from the study prematurely, 18 subjects each from MYL-1701P and Eylea arms. The reasons for early discontinuation of subjects from the study were also comparable between the arms, withdrawal of consent (8 [4.5%] in MYL-1701P arm vs 9 [5.1%] in Eylea arm) being the most common reason followed by withdrawal due to AEs (5 [2.8%] in MYL-1701P arm vs 4 [2.3%] in Eylea arm). Two subjects died in the MYL-1701P arm and three subjects in the Eylea arm. Brief narratives of all deaths and subjects who were discontinued from the study because of AEs up to Week 52 were provided.

There were 4 subjects in the Eylea arm, (3 subjects due to Death, and one subject Withdrew consent), who completed the study treatment, but discontinued the study prior to completing Week 52/EOS visit.

Incidence of TEAEs leading to treatment discontinuation reported in the safety population are summarized in Table 42.

With respect to ocular TEAEs leading to treatment discontinuation, only one such event occurred in the Eylea arm. No such event was identified in the MYL-1701P arm.

IP discontinuation due to a TEAE was reported in both treatment arms in each 3 subjects, i.e. in total in 6/354 (1.7%) subjects. Upon request, the Applicant clarified that only 5 of those subjects were also discontinued from the study. A further 4 subjects were withdrawn from study due to an AE, leading to a total of 9 subjects discontinued study due to a TEAE, as indicated in Table 3 (Section *Results – Participant flow*).

Table 42: TEAEs leading to IP Discontinuation by SOC and PT – Safety Set

System Organ Class [a] Preferred Term [a]	MYL-1701P N=178)		Eylea N=176)		Overall N=354)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any TEAE	3 (1.7)	3	3 (1.7)	4	6 (1.7)	7
Any Non-Ocular TEAE	3 (1.7)	3	2 (1.1)	3	5 (1.4)	6
Nervous system disorders	1 (0.6)	1	1 (0.6)	1	2 (0.6)	2
Embolic stroke	0	0	1 (0.6)	1	1 (0.3)	1
Thrombotic cerebral infarction	1 (0.6)	1	0	0	1 (0.3)	1
Cardiac disorders	0	0	1 (0.6)	1	1 (0.3)	1
Cardiac arrest	0	0	1 (0.6)	1	1 (0.3)	1
Metabolism and nutrition disorders	1 (0.6)	1	0	0	1 (0.3)	1
Hypokalaemia	1 (0.6)	1	0	0	1 (0.3)	1
Neoplasms benign, malignant and unspecified (incl cysts & polyps)	0	0	1 (0.6)	1	1 (0.3)	1
Adenocarcinoma gastric	0	0	1 (0.6)	1	1 (0.3)	1
Renal and urinary disorders	1 (0.6)	1	0	0	1 (0.3)	1
Renal impairment	1 (0.6)	1	0	0	1 (0.3)	1
Any Ocular TEAE – Study Eye	0	0	1 (0.6)	1	1 (0.3)	1
Eye disorders	0	0	1 (0.6)	1	1 (0.3)	1
Macular hole	0	0	1 (0.6)	1	1 (0.3)	1

TEAE = Treatment Emergent Adverse Events. N=number of subjects in the treatment group analysis set. Classifications of adverse events are based on the MedDRA (version 24.1). Percentage (%) based on number of subjects in the row category/N within the column category. [a] Totals for the number of subjects at SOC level are not necessarily the sum of those at the PT levels since a subject may report two or more different adverse events within the SOC level category. An AE is defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing disease) is on or after the first administration of MYL-1701P or Eylea after randomization through EOS/ET. Source: Table 14.3.1.6b and Listing 16.2.7.3b

2.4.7.8. Post marketing experience

This section is not applicable as MYL-1701P has not been approved or marketed yet in any country worldwide.

As a Yesafili biosimilar to Eylea, MYL-1701P has been developed for use in the same adults indications approved for Eylea in the EU. It is a regulatory requirement of biotechnology-derived products to undertake post-marketing activities, including routine pharmacovigilance activities, such as periodic safety update reporting. Any additional risk minimization activities that may be required will be described in a Risk Management Plan (RMP) in accordance with the EMA guidelines [EMA/CHMP/BMWP/403543/2010; EMEA/CHMP/BMWP/14327/2006 Rev 1].

2.4.8. Discussion on clinical safety

In pivotal Phase 3 study MYL-1701P-3001 the safety analysis set consisted of all subjects who received at least one dose of study drug. Of 355 randomized subjects, one subject randomized to the MYL-1701P arm withdrew consent to participate before receiving a dose of the study drug, and was therefore not included in the safety analysis set. Treatment duration, extent of exposure, patient disposition and baseline characteristics were overall comparable between treatment arms. The majority of patients completed week 52 in both study arms. The provided safety database is therefore considered sufficient to assess the comparability regarding common (≥1/100 to <1/10) and very common (≥1/10) adverse events during biosimilar development.

The overall incidence of TEAE was comparable between the study arms and the majority of TEAE was mild to moderate in severity. IP discontinuation due to a TEAE was reported in both treatment arms in each 3 subjects, i.e. in total in 6 subjects. Only 5 of those subjects were also discontinued from the study. A further 4 subjects were withdrawn from study due to an AE, leading to a total of 9 subjects discontinued study due to a TEAE.

Non-ocular TEAEs were overall comparable between the treatment groups. However, more subjects treated with MYL-1701P reported SOC infections and infestations [55/178 (30.9%)] compared to subjects in the Eylea group [41/176 (23.3%)], along with corresponding PT nasopharyngitis (7.9% vs 5.7%), sinusitis (2.2% vs 1.1%), bronchitis, influenza and pneumonia (in each 2.2% vs 0.6%) and respiratory tract infection (1.1% vs 0%). Further, the more frequently occurring PT pyrexia (3.9% vs 1.7%) and cough (3.4% vs 0.6%) may indicate a higher incidence in the risk of (especially respiratory tract) infections. No ADRs related to the respiratory system are currently stated in section 4.8 of provided SmPC or in SmPC of Eylea. The observed higher incidence of reported infections as well as higher incidence of reported peripheral swelling (2.8% vs 0%) and fall (3.9% vs 0.6%) in the MYL-1701P arm was not considered to impact the conclusion on similar safety, as those events were mostly mild to moderate in severity, not related to study drug and concerned few patients.

Apart from those, other non-ocular TEAEs were reported in both groups at similar frequencies and no further concerns arise from these findings.

The overall incidences of **ocular TEAE** in the study eye were highly similar between treatment arms [55/178 (30.9%) and 52/176 (29.5%) of subjects in the MYL-1701P and Eylea group, respectively]. Of those, cataract was reported more frequently in the MYL-1701P arm, while others were more frequently observed in the Eylea arm. In the study eye, **severe ocular TEAEs** were reported in one (0.6%) subject (PT: posterior capsule opacification) in the MYL-1701P arm and 3 (1.7%) subjects (PTs: macular hole, and vitreous detachment, vitreous detachment, cataract) in the Eylea arm. No ocular life-threatening ocular TEAEs were reported. The observed ocular TEAEs are listed ADR in the

Eylea SmPC and therefore within the expected safety profile of Eylea and overall comparable between treatment arms.

All the definitely **related TEAEs** were ocular TEAEs in study eye. Most of those are known undesirable effects of Eylea (SmPC), except papilledema, which occurred in the MYL-1701P treatment arm as a single AE of moderate severity, which occurred eight days after the first dose of MYL-1701P and resolved following treatment with cetirizine, topical dexamethasone and topical nepafenac. In general, reported drug related TEAEs (≥ 2 subjects by PT) are known undesirable effects of Eylea (SmPC), and appear to be less common in the MYL-1701P arm.

Major adverse cardiovascular events (**MACE**) have been reported as adverse events of interest, since there is a theoretical risk of cardiovascular effects upon systemic anti-VEGF treatment. In total, nine events were classified as MACE and numerically more MACE occurred in the Eylea arm. Of those, one event each of cardiac arrest, embolic stroke and brain stem infarction in the Eylea arm were classified possibly related to the study drug. Although cardiac arrest and embolic stroke were considered non-fatal, the subject (Eylea arm) died after withdrawal from study. No concerns regarding the assessment of biosimilarity arises from those events, since overall mean concentrations of systemic aflibercept at expected Cmax were comparable in the PK subset of patients, and no association of high systemic aflibercept and the occurrence of MACE was observed.

The occurrence of other AE of special interest, **ocular injection procedure related TEAEs**, was in line with known undesirable effects of Eylea (SmPC) and comparable between treatment arms.

Overall, there were more subjects with **serious TEAEs** for MYL-1701P [31/178 (17.4%)] compared to Eylea [23/176 (13.1%)]. Numerically the highest difference was reported for PT infections and infestations. Similar to overall non-ocular TEAEs and as discussed above, as these events had different origins, no single type of infection could be identified. Hence, the overall higher incidence in the MYL-1701P group may be a chance finding. Similarly, most serious TEAE were reported in both groups and at low numbers per PT. Three serious ocular TEAEs were reported, 1 in the MYL-1701P arm and 2 in the Eylea arm. The overall safety profile of serious TEAEs seems thus acceptable and comparable in both treatment arms.

In total, 6 patients **died** during or after the study, 2 in the MYL-1701P arm and 4 in the Eylea arm. Narratives for all patients have been provided by the Applicant. All the events leading to death were considered not related to the study drug by the Investigator, which can be followed. All patients had prior/concomitant co-morbidities and two subjects died from COVID19 infections. One subject (Eylea arm) had Grade 4 SAE cardiac arrest and embolic stroke, which were considered possibly related to the study drug, and led to discontinuation from study after they had been resolved. Death occurred after the subject was withdrawn from the study. No concerns regarding aflibercept treatment arise from these fatal events.

Taken together, the safety profile of MYL-1701P and Eylea is acceptable, in line with known undesirable effects of Eylea, and comparable between study arms. While numerically some TEAEs are reported more frequently in the MYL-1701P arm, most relevant (ocular, related, severe) TEAEs are reported more frequently in the Eylea arm.

Laboratory findings

Hematology and serum chemistry mean laboratory parameters were comparable between treatment arms and no trends or notable shifts from normal were observed. By Week 52, HbA1c had shifted from normal to high more frequently in the Eylea arm. Urinalysis data and vital signs were comparable between treatment arms. No clinically meaningful trends were noted for ECG parameters between the study arms. Clinically significant abnormal ECG was observed in similar proportions of subjects between the study arms throughout the study duration.

As expected, mean IOP increased after intravitreal injection, and returned to baseline until the subsequent pre-dose measurement. Pre- and post-dose mean values as well as mean differences pre- and post-dose were similar between study arms. Increased IOP was experienced by 4 (2.2%) subjects treated with MYL-1701P vs 3 (1.7%) subjects treated with Eylea. IOP is a known common (≥1/100 to <1/10) undesirable effect of Eylea, and hence the incidence in both study arms was in line with the expected safety profile. Clinically significant abnormal findings from indirect ophthalmoscopy and slit-lamp biomicroscopy are reported as AEs, which is considered appropriate.

In conclusion, no safety concerns arise from laboratory findings, which were similar between study arms.

Immunogenicity

At baseline, similar proportions of patients were positive for ADA: 17/178 (9.6%) of subjects in the MYL-1701P group compared to 18/176 (10.2%) in the Eylea group. One subject was positive for NAb (MYL-1701P group). The overall incidence of ADA positive subjects at baseline was higher compared to what was observed in registrational Eylea studies (VIVID/VISTA), which may be explained by different sensitivity and specificity of the assays used.

Throughout the study duration the proportion of ADA positive subjects remained similar in both treatment groups. Treatment induced or treatment boosted ADA were overall rare and only transiently observed in some patients. Likewise, the overall rare occurrence of NAbs was transient in most cases, and not observed in treatment induced or boosted ADA positive subjects, except 1 subject in the Eylea arm having treatment boosted ADA. Mean ADA titers were generally lower in the MYL-1701P treatment arm compared to Eylea. From Week 40, mean titers were more than 5-fold lower in the MYL-1701P group. This difference along with the observed high SD in the Eylea group can be explained by exceptionally high titers in few subjects. Reduced efficacy, as assessed by BCVA and CRT, was only observed in one subject with the highest ADA titer (>1:1000).

Neither the change in BCVA from baseline nor equivalence was compromised by the occurrence of ADA. In fact, at Week 8 the mean change from baseline in BCVA was even higher and very similar in both treatment arms in the ADA positive subgroup in a descriptive analysis. No clinically relevant trends were observed in specific NAb positive subjects with respect to BCVA gain or CRT reduction over time during the study. Overall, no clinically relevant differences in the overall incidence of TEAEs was observed between ADA positive and ADA negative subjects or between study arms. In addition, the comparison of TEAE profiles of treatment-induced and treatment-boosted ADA/NAb positive subjects to those of ADA/NAb-negative subjects did not reveal any comprehensive findings.

Taken together, overall immunogenicity appears lower in patients with MYL-1701P treatment compared to Eylea and no impact on efficacy or safety was observed upon occurrence of ADA.

2.4.9. Conclusions on the clinical safety

The overall safety profile of Yesafili (MYL-1701P) is in line with known adverse events of Eylea (SmPC). Some events were reported more frequently in the MYL-1701P arm, while others were more frequent in the Eylea arm, but no significant differences were observed. Therefore, biosimilarity is supported from a safety perspective. The overall immunogenicity profile appears to be lower for MYL-1701P compared to Eylea.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of 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

Table 43: Summary table of pharmacovigilance activities and risk minimisation measures by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Endophthalmitis (likely infectious origin)	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3 and 4 Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: None
Intraocular inflammation	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet section 2, 3 and 4 Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: None
Transient intraocular pressure increase	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet section 2 and 4 Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: None
Retinal pigment epithelial tears	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Package Leaflet section 2 and 4 Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: None
Cataract (especially of traumatic origin)	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 Package Leaflet section 2, 3 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Additional pharmacovigilance activities: None
Medication errors	Routine risk minimization measures: SmPC sections 4.2, 4.9 and 6.6 Package Leaflet section 1 and 3 Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: None
Off-label use and misuse	Routine risk minimization measures: SmPC sections 4.1, 4.3, 4.4 and 4.6 Package Leaflet section 1, 2 and 3 Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: None
Embryo-fetotoxicity	Routine risk minimization measures: SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 Additional risk minimisation measures: Prescriber guide and patient guide and its audio version	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Additional pharmacovigilance activities: None

Conclusion

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

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.7.2. Additional monitoring

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

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Yesafili (MYL-1701P; M710) is developed as a biosimilar to the reference product Eylea. The intravitreal route of administration, posology, and adult indications are identical to the reference product as described in the Eylea SmPC. Yesafili will be available in vials only, whereas Eylea is available in vials and pre-filled syringes (PFS).

The marketing authorization is claimed for treatment of adults with

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

Quality

The Applicant performed a comprehensive analytical biosimilarity exercise comparing Yesafili (MYL-1701P), the reference medicinal product EU-Eylea, and US-Eylea that was used in the pivotal clinical study MYL-1701P-3001. A sufficient number of MYL-1701P and Eylea lots, which can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product, was included.

The relevant quality attributes of the aflibercept molecule were assessed using a broad panel of orthogonal standard and state-of-the art techniques. Analyses covered primary sequence and higher order structure, size and charge variants, glycosylation and other post-translational modifications, as well as protein concentration. Functional activity was compared by a large panel of binding assays and cell-based biological assays covering the mode of action for the targeted indications and Fc-related functions. Based on the provided information, it is concluded that the analytical methods are suitable and sensitive to detect minor differences.

The quality attributes were either evaluated against a quality range or assessed qualitatively. Generally, the applied similarity criteria were insufficiently justified for several quality attributes. However, analytical results including chromatograms, spectra, response curves etc. for the individual lots have been provided, which enabled an independent assessment of the available data.

Summary of clinical data

Study **MYL-1701P-3001** evaluated the clinical similarity of Yesafili (MYL-1701P; M710) and Eylea with regards to efficacy, safety, pharmacokinetics and immunogenicity in the treatment of subjects with DME. The study was a multi-center, (1:1) randomized, double masked, active controlled, comparative clinical trial to demonstrate that no clinically meaningful differences exist between Yesafili and US-licensed Eylea in 355 subjects with DME treated up to 52 weeks. In total, application of 9 doses was scheduled (5 doses monthly, followed by 4 doses bi-monthly) to be administered via intravitreal injections of either 2 mg Yesafili or 2 mg US-Eylea. Additional doses were permitted upon worsening of the condition.

Pharmacokinetics (free aflibercept concentrations) was evaluated for 89 patients participating in a PK subset of this study.

The design of the clinical study has been discussed in Scientific Advices, which were largely adhered to by the Applicant.

3.2. Results supporting biosimilarity

Quality

For most quality attributes including multiple attributes covering the mechanism of action, high analytical similarity of Yesafili (MYL-1701P) to the reference product EU-Eylea has been demonstrated. The observed analytical differences have been adequately justified and they are not expected to have a relevant impact on clinical performance of the product.

Analytical comparability of EU-Eylea and US-Eylea has been satisfactorily demonstrated.

Clinical

Efficacy

Primary endpoint: In the ITT analysis set, the adjusted mean difference for the mean change in BCVA from baseline to Week 8 was 0.04 letters and the corresponding 95% CI was [-1.40, 1.47] which was well within the pre-defined and accepted equivalence range of [-3, +3] letters. In the PP analysis set, which is also considered primary by the Rapporteur, the adjusted mean difference for the mean change in BCVA from baseline to Week 8 was -0.19 letters and the corresponding 95% CI was [-1.66, 1.27] which was also fully contained within the pre-defined and accepted equivalence range.

Key secondary endpoint: In the ITT analysis set, the mean treatment difference for the mean change in CRT from baseline up to Week 8, was 11.46 µm and the 95% CI was [-6.22 µm, 29.14 µm]. While an equivalence range was not defined for CRT, the 95% CI indicated no clinically relevant difference between the treatment groups. The mean change in CRT throughout the entire study duration indicated an increase of improvement (change from baseline) in both study arms over time.

Other secondary endpoints: The mean change in BCVA over time up to Week 52 (ITT set) shows similar responses between the two treatment arms across visits. The proportion of subjects who gained ≥15 letters at Week 52 were similar between the two treatment arms [33.0% (MYL-1701P) vs. 29.1% (Eylea); The adjusted mean change from baseline of 10.76 letters in the MYL-1701P arm and 10.52 letters in the Eylea arm was however almost the same, such that the dichotomization led to some

difference]. The mean number of doses received during the 52 weeks of study were similar in both treatment arms (8.4 doses in the MYL-1701P arm and 8.7 doses in the Eylea arm).

Ancillary analyses: Sensitivity analyses were conducted for the **primary endpoint** and results of each of these sensitivity analyses supported equivalence between the treatment arms based on that the 95% confidence intervals of the treatment differences being within the pre-specified equivalence range, thus confirming the robustness of the primary analyses. These included, but were not limited to:

- Analysis of the primary endpoint in which BCVA values after discontinuing study medication (i.e., values with an assessment date after the last study medication date) were excluded.
- Tipping point analysis for delta method using multiple imputation.

In addition, several sensitivity and supplementary analyses were conducted to assess the impact due to COVID-19-related disruptions (e.g. missed/delayed visits), most of which showed equivalence between the treatment arms based on the 95% confidence intervals entirely lying within the pre-specified equivalence range.

In the most sensitive subgroup of subjects with baseline BCVA 50-69, the treatment effect was similar to the primary analysis of the overall study population. The mean treatment difference was -0.01 and the 95% CI was [-1.89, 1.86] and therefore within the pre-defined equivalence range of [-3, +3] letters. This subgroup was also the largest (114 subjects in MYL-1701P and 106 subjects in Eylea) and is therefore considered the most relevant in this biosimilar exercise.

Further subgroup analyses (by baseline BCVA, age, gender, race, ethnicity, geographic region, baseline HbA1c, anti-VEGF therapy in fellow eye, ADA) showed that mean change in BCVA from baseline to Week 8 also consistently support equivalence between the treatment arms in subgroups. Similar was seen for subgroup analyses of the **key secondary endpoint** (mean change in CRT from baseline up to Week 8).

PK

Supportive PK analyses were conducted in a subset of patients enrolled in the pivotal clinical study MYL-1701P-3001. As systemic exposure is expected to be low, no formal hypothesis testing was planned. Mean values for plasma concentrations at anticipated maximum systemic exposure were similar in both treatment arms, supporting biosimilarity.

Safety

Overall, 354 subjects (178 in the MYL-1701P arm and 176 in the Eylea arm), received study treatment. The median treatment duration was 364 days in both study arms. 161/179 (89.9%) subjects in the MYL-1701P arm and 158/176 (89.8%) in the Eylea arm completed week 52. The safety database is considered appropriate to assess the comparability of common (≥1/100 to <1/10) and very common (≥1/10) adverse events for a biosimilar development.

The overall incidence of TEAE was comparable between the study arms and the majority of all TEAE was mild to moderate in severity.

Most **non-ocular** TEAE were reported in both groups and in total in a low number of patients. The overall safety profile seems therefore acceptable and comparable in both treatment arms.

The overall incidences of **ocular** TEAEs in the study eye were highly similar between treatment arms: 55/178 (30.9%) and 52/176 (29.5%) of subjects in the MYL-1701P and Eylea group, respectively.

The majority of TEAEs were considered not related [in 231/354 (65.3%) of subjects] or unlikely [28/354 (7.9%) of subjects] related to study drug and there were no notable differences in frequencies

between the treatment arms. All of the definitely related TEAEs were ocular TEAEs in study eye. Most of those are known undesirable effects of Eylea (SmPC).

The occurrence of ocular injection procedure related TEAEs was in line with known undesirable effects of Eylea (SmPC) and highly comparable between treatment arms.

Hematology and serum chemistry mean laboratory parameters were comparable between treatment arms and no trends or notable shifts from normal were observed. Likewise, urinalysis data and vital signs were comparable between treatment arms. Increased IOP was experienced by 4 (2.2%) subjects treated with MYL-1701P vs 3 (1.7%) subjects treated with Eylea.

The safety profile in both study arms was largely in line with the known safety profile of Eylea (SmPC).

Immunogenicity

At baseline, similar proportions of patients were positive for ADA: 17/178 (9.6%) of subjects in the MYL-1701P group compared to 18/176 (10.2%) in the Eylea group. Throughout the study duration the proportion of ADA positive subjects remained similar in both treatment groups.

Neither the change from baseline nor equivalence was compromised by the occurrence of ADA. In fact, at Week 8 the mean change from baseline in BCVA was even higher and very similar in both treatment arms in the ADA positive subgroup. No clinically relevant trends were observed in specific NAb positive subjects with respect to BCVA gain or CRT reduction over time during the study.

Overall, no clinically relevant differences in the incidence of TEAEs was observed between ADA positive and ADA negative subjects or between study arms.

3.3. Uncertainties and limitations about biosimilarity

Quality

The differences observed in biological activity and for the HMW variants have been sufficiently justified. An impact on clinical performance is not expected.

Clinical

Efficacy

Other secondary endpoints: Although the median number of doses received during the 52 weeks of study was nine in both treatment arms, the median of discrete numbers is an insensitive metric, and indeed only 56.3% of all patients received nine doses, as planned per study protocol. Reassuringly, only few of those patients received additional doses due to worsening of their condition, since the majority of patients who received 9 doses have not received any additional dose (95%). More patients in the MYL-1701P arm received additional doses of aflibercept (30.3%) compared to subjects receiving Eylea (23.9%), which is partially attributed to more optional doses received after a missed planned dose in patients in the MYL-1701P arm, rather than worsening of their condition. A slightly higher proportion of subjects in the Eylea arm received less than 9 planned doses.

Ancillary analyses:

In some subgroup analyses the sample size was too low to for a meaningful interpretation of analysis results as these led to wide 95% CIs and thereby extending across the equivalence range.

Safety

The safety database is considered sufficient to assess the comparability regarding 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.

More subjects experienced at least one related TEAE in the Eylea arm [12/176 (6.8%)] compared to MYL-1701P [5/178 (2.8%)]. Similarly, 3/176 (1.7%) experienced a related serious TEAE in the Eylea arm compared to zero in the MYL-1701P group.

More subjects treated with MYL-1701P reported **non-ocular** TEAEs for SOC infections and infestations [55/178 (30.9%)] compared to subjects in the Eylea group [41/176 (23.3%)], along with corresponding PT nasopharyngitis (7.9% vs 5.7%), sinusitis (2.2% vs 1.1%), bronchitis, influenza and pneumonia (in each 2.2% vs 0.6%), respiratory tract infection (1.1% vs 0%), pyrexia (3.9% vs 1.7%) and cough (3.4% vs 0.6%).

Numerically higher incidences of non-ocular TEAE in the MYL-1701P arm were also observed for SOC investigations, metabolism and nutrition disorders, gastrointestinal disorders, renal and urinary disorders, general disorders & administration site conditions, injury, poisoning and procedural complications, and respiratory, thoracic and mediastinal disorders. On the other hand, Eylea treated subjects more frequently reported SOC vascular disorders, nervous system disorders, muscoskeletal & connective tissue disorders, and blood and lymphatic system disorders. However, most of these TEAEs per PT occurred in only few patients and at comparable frequencies between treatment arms per PT.

The **ocular** TEAE cataract was reported more frequently in the MYL-1701P arm [11/178 (6.2%) subjects] compared to the Eylea group [6/176 (3.4%) subjects].

Most of definitely related ocular TEAEs are known undesirable effects of Eylea (SmPC), except papilledema, which occurred at a single occasion in the MYL-1701P treatment arm.

The frequency of drug related TEAEs (≥ 2 subjects by PT) was higher in Eylea treated subjects [12/176 (6.8%)] compared to the MYL-1701P arm [5/178 (2.8%)].

Nine events were classified as MACE and occurred in seven subjects, more frequently in the Eylea arm [5/176 (2.8%)] compared to the MYL-1701P arm [2/178 (1.1%) subjects].

Overall, there were more subjects with serious TEAE for MYL-1701P [31/178 (17.4%)] compared to Eylea [23/176 (13.1%)].

By Week 52, HbA1c had shifted from normal to high more frequently in the Eylea arm. Abnormal ECG interpretation was observed more frequently in the MYL-1701P arm throughout the study duration, but was considered not clinically significant in the majority of subjects.

Immunogenicity

2.8% subjects in MYL-1701P arm and 5.7% subjects in Eylea arm reported either treatment induced (developed any time after the initiation of drug administration in a subject without pre-existing ADA) or treatment boosted ADA (titer was at least 4 times the baseline titer in a subject who had a pre-existing ADA). Some of these subjects had positive ADA only transiently at specific visits. Overall, 2 subjects in MYL-1701P and 5 subjects in Eylea arm tested positive for NAb at least in one of the post-baseline visits, but the occurrence of NAb was transient in most cases, and not observed in treatment induced or boosted ADA positive subjects, except 1 subject in the Eylea arm having treatment boosted ADA. Mean ADA titers were generally lower in the MYL-1701P treatment arm compared to Eylea.

Overall, immunogenicity appears to be lower in patients with MYL-1701P treatment compared to Eylea.

3.4. Discussion on biosimilarity

Overall, at the quality level similarity between MYL-1701P (M710) and EU-sourced Eylea could be demonstrated for most quality attributes in a comprehensive analytical similarity exercise. Comparability between EU- and US-sourced Eylea, which was used as comparator in the pivotal clinical trial, could be demonstrated in the analytical similarity exercise. The observed differences have been adequately justified and are not expected to impact clinical performance of the product.

The pivotal clinical study MYL-1701P-3001 was adequately designed to demonstrate equivalence between Yesafili (MYL-1701P) and US-Eylea on an efficacy level, as well as safety. The selected study population of patients with DME, as well as primary and secondary efficacy endpoints are deemed appropriate for this biosimilarity exercise. The primary efficacy endpoint, change in BCVA from baseline to Week 8, was well within the pre-defined equivalence range of +/- 3 letters and demonstrated equivalent efficacy in the primary endpoint. Biosimilarity was further confirmed by secondary endpoints, which included change in CRT and BCVA over time.

The overall safety profile appears comparable between Yesafili and Eylea and was largely in line with the known safety profile of Eylea (SmPC) in both study arms. Adverse events were equally reported more frequently in the Yesafili arm or in the Eylea arm, with no observable pattern favouring either of the two. Most observed imbalances between the treatment groups concern only few patients and events and should therefore be interpreted with caution and not be overinterpreted. Immunogenicity is overall observed to be somewhat lower after MYL-1701P treatment, but this is likely a chance finding due to overall very low and transient occurrence of treatment induced or treatment boosted ADA, or NAb. The occurrence of ADA did not compromise the change in BCVA from baseline in either treatment arm or equivalence. PK analyses conducted in a subset of patients within the pivotal study are appropriate and the comparable PK results with little systemic availability do support biosimilarity.

Overall, the clinical data suggest biosimilarity between Yesafili (MYL-1701P) and US-Eylea regarding efficacy and safety, as well as PK.

3.5. Extrapolation of safety and efficacy

The Applicant is seeking approval of Yesafili (MYL-1701P) in all adults indications, for which Eylea is approved. The Yesafili (MYL-1701P) program provides clinical data from a pivotal study in patients with DME. The mechanism of action of Eylea in DME is representative of the mechanism of action of Eylea in all other adults indications for which Eylea is approved. VEGF plays a central role in the pathogenesis of DME, wAMD, RVO, and myopic CNV. In each of these patient populations, aflibercept is understood to act as a soluble decoy receptor that inhibits the receptor binding of VEGF-A and PlGF and subsequently the angiogenic downstream signal cascade and functional activities.

Highly sensitive *in vitro* assays were used to measure biological activities known to be critical to the mechanism of action of aflibercept with multiple batches of MYL-1701P and Eylea.

The justification presented by the Applicant to allow extrapolation from DME to all approved adults indications of Eylea is considered adequate.

3.6. Additional considerations

Establishment of the aflibercept (MYL-1701P) drug substance process control strategy followed an enhanced development approach and heavily depends on qualification of the used small-scale models (SSM) and the outcome of the process characterisation studies. In addition, adequate qualification of the SSM is also essential for validity of the virus clearance studies. At D120 a Major Objection was

raised in relation to the SSMs and process characterisation. The issues raised in the Major Objection have been satisfactorily addressed during the procedure.

3.7. Conclusions on biosimilarity and benefit risk balance

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

Yesafili 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 Yesafili. 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 Yesafili is marketed, ophthalmological clinics where Yesafili is expected to be used are provided with an updated physician information pack containing the following elements:

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

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

- Techniques for the intravitreal injection including use of a 30 G needle and angle of injection
- Confirmation that the vial is for single use only
- The need to expel excess volume of the syringe before injecting Yesafili 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 Yesafili

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

- Patient information leaflet
- Who should be treated with Yesafili
- How to prepare for Yesafili treatment
- What are the steps following treatment with Yesafili
- 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 Yesafili