12 December 2024
EMA/1268/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eydenzelt

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/005899/0000

Note

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

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Administrative information

Name of the medicinal product:	Eydenzelt
Applicant:	Celltrion Healthcare Hungary Kft. Vaci Ut 1-3 1062 Budapest VI HUNGARY
Active substance:	aflibercept
International Non-proprietary Name/Common Name:	aflibercept
Pharmaco-therapeutic group (ATC Code):	ocular vascular disorder agents, antineovascularisation agents (S01LA05)
Therapeutic indication(s):	Eydenzelt 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).
Pharmaceutical form(s):	Solution for injection
Strength(s):	40 mg/ml
Route(s) of administration:	Intravitreal use
Packaging:	pre-filled syringe (plastic) and vial (glass)
Package size(s):	1 pre-filled syringe and 1 vial + 1 filter needle

Table of contents

List of abbreviations

AMD	Neovascular (wet) age-related macular degeneration
%CV	Relative coefficient of variation
4-PL	4-parameter logistic
ACE	Affinity capture elution
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
aDP	Assembled drug product
AE	Adverse event
AESI	Adverse event of special interest
AET	Analytical evaluation threshold
AEX	Anion exchange chromatography
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
ATE	Arterial thromboembolic event
AUC	Analytical ultracentrifugation
$AUC_{0\text{-}672hr}$	Area under the plasma concentration-time curve from 0 to 672 hours
BCVA	Best corrected visual acuity
BLGF	Break-loose and gliding force
BLQ	Below lower limit of quantitation
BPD	Biological Product Development
BRVO	Branch retinal vein occlusion
C1q	Complement component 1q
CAS	Chemical Abstracts Service
CCS	Container closure system
CD	Circular dichroism spectroscopy
CDC	Complement-dependent cytotoxicity
CE-SDS	Capillary electrophoresis using sodium dodecyl sulfate non-gel sieving
CEX	Cation exchange chromatography
CFR	Code of federal regulations
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CIPT	Critical in-process test
CLT	Celltrion
C_{max}	Maximum plasma concentration
Cmax	Maximum concentration

CMC	Chemistry, Manufacturing and Control
CNV	Choroidal neovascularization
COP	Cyclo olefin polymer
COVID-19	Coronavirus disease of 2019
CPP	Critical process parameter
CQA	Critical quality attribute
CRO	Contract research organization
CRVO	Central retinal vein occlusion
CSR	Clinical study report
CST	Central subfield thickness
CTCAE	Common terminology criteria for adverse event
CT-P42	Eydenzelt, aflibercept of Celltrion Healthcare
CV%	Percent of coefficient of variation
DM	Diabetes mellitus
DME	Diabetic macular oedema
DNA	Deoxyribonucleic acid
DP	Drug product
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
DS	Drug substance
DSC	Differential scanning calorimetry
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency
EOS	End-of-Study
EOS1	the first End-of-Study
EOS2	the second End-of-Study
EPCB	End-of-production cell bank
ERG	Electroretinography
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
F	Female
F/T	Freeze and thaw
FAS	Full Analysis Set
Fc	Fragment crystallisable region
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
fDP(-TS)	Finished drug product (terminally sterilised)
ffERG	Full-field electroretinography
FLD	Fluorescence detection

FTIR	Fourier-transformed infrared spectroscopy
FU	Follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAP	Hamster antibody production test
HbA1c	Haemoglobin A1c
HCCF	Harvested cell culture fluid
HCP	Host cell protein
HF	Human factor
HILIC	Hydrophilic interaction liquid chromatography
HMW	High molecular weight (variant)
HPLC	High performance liquid chromatography
HQC	High quality control
hr(s)	Hour(s)
HUVEC	Human umbilical vein endothelial cell
hVEGF	human vascular endothelial growth factor
ICH	International Council for Harmonisation
IFU	Instructions for use
IGF	Insulin-like growth factor
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IND	Investigational New Drug
INN	International non-proprietary name
IOP	Intraocular pressure
IPM	In-process monitoring
IPT	In-process test
ITT	Intent-to-Treat
IVT	Intravitreal
LC-MS	Liquid chromatography mass spectrometry
LER	Low endotoxin recovery
LIVCA	Limit of in vitro cell age
LLoQ	Lower limit of quantification
LMW	Low molecular weight (variant)
LQC	Low quality control
LRF	Log reduction factor
LRV	Log reduction value
LS	Least squares
M	Male
MAA	Marketing Authorisation Application
MALS	Multi-angle light scattering
MAP	Mouse antibody production test

MAR	Missing at random
Max	Maximum
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MF	Male and female combined
MI	Multiple imputation
Min	Minimum
min(s)	Minute(s)
MoA	Mechanism of action
MP	Monitored parameter
MS	Mass spectrometry
MSD	Meso scale discovery
MuLV	Murine leukaemia virus
MVM	Minute virus of mice
N.C	Not calculable
NAb	Neutralising antibody
NF	National formulary
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OCT	Optical coherence tomography
OD	Oculus dexter (right eye)
OECD	Organization for Economic Co-operation and Development
OOS	Out-of-specification
OS	Oculus sinister (left eye)
P	Passage
PC	Polycarbonate
PD	Pharmacodynamic(s)
PDE	Permitted daily exposure
PFS	Prefilled syringe
Ph. Eur.	European pharmacopoeia
PHS	Public Health Service
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PlGF	Placental growth factor
PP	Per-Protocol
PPQ	Process performance qualification
PRCB	Primary research cell bank
PRS	Primary reference standard
PRV	Pseudorabies virus
PT	Preferred term
QA	Quality attribute
QC	Quality control

QTPP	Quality target product profile
Red.	Reducing
Reo-3	Reovirus type 3
RLU	Relative light unit
RMP	Reference medicinal product
ROP	Retinopathy of prematurity
RP	Reversed phase
RS	Reference standard
RT	Reverse transcriptase
RTRT	Real-time release testing
RVO	Retinal vein occlusion
SA	Scientific advice
SAE	Serious adverse event
SAP	Statistical analysis plan
SCC	Single cell clone
SD	Standard deviation
SDM	Scale-down/small-scale model
SE	Standard error
SEC	Size exclusion chromatography
SOC	System organ class
SPA	Special protocol assessment
SPR	Surface plasmon resonance
SRF	Subretinal fluid
SST	System suitability test
SU	Single-use
SUP	Single-use plant
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
TEM	Transmission electron microscopy
TESAE	Treatment emergent serious adverse event
TK	Toxicokinetic(s)
T_{max}	Time to maximum plasma concentration
Tmax	Time to maximum concentration
TS	Terminal sterilisation
uDP	Unlabelled drug product (for drug product Vial)
uDP	Unassembled drug product (for drug product PFS)
uDP-TS	Unassembled drug product terminally sterilised
UF/DF	Ultrafiltration/diafiltration
ULOQ	Upper limit of quantification
UPLC	Ultra performance liquid chromatography
US	United States

USP	United states pharmacopoeia
USPI	United States prescribing information
UV	Ultraviolet
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VEP	Visual evoked potential
VHL	Vitreous humour left
VHR	Vitreous humour right
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 23 November 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Eydenzelt, through the centralised procedure falling within the Article 3(1) and point 1of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 March 2021.

The applicant applied for the following indication:

Eydenzelt 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 product.

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

The chosen reference product is:

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

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

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

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

- Marketing authorisation number: EU/1/12/797/001-002

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

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

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Reference	Date	SAWP co-ordinators
EMEA/H/SA/4380/1/2020/III	27/02/2020	Dr Stephan Lehr and Dr Kerstin Wickström
EMA/317759/2020	10/07/2020	Dr Stephan Lehr and Dr Kerstin Wickström
EMEA/H/SA/4380/1/FU/1/2020/II	15/10/2020	Prof Andrea Laslop and Dr Kerstin Wickström

The applicant received scientific advice on the development of aflibercept biosimilar to Eylea from the CHMP on 27 February 2020 (EMEA/H/SA/4380/1/2020/III). The Scientific Advice pertained to the following quality/non-clinical/clinical aspects:

• Comparability strategy and stability tests

• Overall nonclinical development approach

• Choice of comparator and study design (duration, number of patients, statistical analysis, inclusion criteria)

The applicant received a clarification on scientific advice on the development of aflibercept biosimilar to Eylea from the SAWP on 10 July 2020 pertaining to the following clinical topic.

- Inclusion and exclusion criteria for the Phase III study.

The applicant received scientific advice on the development of Aflibercept a biosimilar to Eylea from the CHMP on 15 October 2020 (EMEA/H/SA/4380/1/FU/1/2020/II). The Scientific Advice pertained to the following clinical aspects:

• The design of the revised Phase III comparative study including the sample size and power, the inclusion/exclusion criteria, assessments.

• The sufficiency of the safety database to characterise the safety and immunogenicity profile.

of CT-P42 as biosimilar aflibercept.

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: Antonio Gomez-Outes

The application was received by the EMA on	23 November 2023
The procedure started on	28 December 2023
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	18 March 2024
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	2 April 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	12 April 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 July 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	26 August 2024

The following GMP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GMP inspection at Celltrion Inc., 23, Academy-ro, Yeonsugu, Incheon, 22014, Republic of Korea, with manufacturing of drug substance, quality control testing of drug substance and quality control testing of drug product in scope, conducted between 22nd and 31st of May 2024. The positive outcome of inspection was issue on	30 August 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	05 September 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	12 November 2024
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	27 November 2024
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 Eydenzelt on	12 December 2024

2. Scientific discussion

2.1. About the product

Eydenzelt (also referred as CT-P42) 40 mg/mL solution for injection (in pre-filled syringe and vial) has been developed as a biosimilar to the reference product Eylea (INN: aflibercept; EMEA/H/C/002392).

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

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

The claimed therapeutic indications for Eydenzelt are:

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

2.2. The development programme/compliance with guidance/scientific advice

Scientific advice: during the development of CT-P42 a written scientific advice has been obtained from the European Medicines Agency (EMA).

2.3. Quality aspects

2.3.1. Introduction

Eydenzelt (laboratory code CT-P42) has been developed as a similar biological medicinal product to the reference medicinal product, Eylea (EMEA/H/C/002392).

The finished product is presented as a solution for intravitreal injection with 40 mg/mL aflibercept in a single-use Type I glass vial (nominal content 100 µL) with a rubber stopper and flip-off cap and co-packaged stainless steel filter needle or in a pre-filled syringe (PFS; nominal content 90 µL) made of cyclo olefin polymer with rubber plunger stopper and tip cap. One dose corresponds to 50 µL containing 2 mg aflibercept.

Other ingredients are: histidine, histidine hydrochloride monohydrate, sodium chloride, trehalose, polysorbate 20, and water for injections.

The formulation of the finished product in the vial and the PFS is identical.

The product is available as vial-kit or PFS as described in section 6.5 of the SmPC:

2.3.2. Active substance

2.3.2.1. General Information

The active substance of CT-P42 is aflibercept (INN), a recombinant fusion protein consisting of two identical peptide chains linked by disulfide bonds. Each chain consists of domain 2 from human VEGFR-1 and domain 3 from VEGFR-2, that is fused to the Fc portion of human IgG1. The molecular mass of the de-glycosylated is 96.897 kDa.

Aflibercept exerts its therapeutic effects by binding to vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF) thereby inhibiting the binding and activation of their cognate VEGF receptors, i.e. VEGF receptor 1 (VEGFR-1; VEGF, PlGF) and VEGF receptor 2 (VEGFR-2; VEGF). Activation of these receptors by VEGF-A can result in neovascularization and excessive vascular permeability.

Beyond the antagonistic effect against VEGF family members, it has been recently reported that aflibercept also binds to and blocks galectin-1 that plays a crucial role in promoting angiogenesis in anti-VEGF-A refractory tumours.

Fc-related effector functions are not involved in the mechanism of action (MoA).

2.3.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Active substance (AS) is manufactured by Celltrion Inc. (Plant I), Yeonsu-gu, Incheon, 22014, Republic of Korea and released by Celltrion Inc. (Plant II), Yeonsu-gu, Incheon, 22014, Republic of Korea. Satisfactory demonstration of GMP compliance has been provided.

The active substance of CT-P42, i.e. aflibercept, is expressed in a CHO cell line and produced in a fed-batch process. Manufacture of a batch starts from a single vial of the working cell bank (WCB). After thawing, cells are expanded in inoculum expansion steps and the seed bioreactor step under controlled conditions. Inoculum expansion includes serial sub-cultivations in shake flasks, in the seed bioreactor step cells are expanded in a single-use (SU) bioreactor operated in batch mode. Upon transfer into a SU production bioreactor, cells are finally expanded and maintained under controlled conditions. The harvest procedure includes a series of filtrations.

CT-P42 is purified from the HCCF by a combination of three column chromatography steps, i.e. Protein A affinity chromatography, cation exchange chromatography, and multimodal anionic-exchange chromatography. Multiple chromatography cycles may be performed per AS batch at each step. Chromatography resins and the ultrafiltration/diafiltration (UF/DF) membrane are re-used for multiple cycles. Two dedicated, orthogonal virus clearance steps are integrated into the purification process.

The virus filtration pool is concentrated and conditioned by stepwise UF/DF. Prior to filling into gamma-sterilised polycarbonate (PC) bottles, the adjusted UF/DF pool is finally filtered.

The applicant provided a detailed description of the manufacturing process steps that is accompanied by flow charts including process parameters (critical/non-critical) and in-process control tests (critical/non-critical) and their acceptable range/acceptance criteria as well as a description of the hold times. Overall, the process description is in line with regulatory expectations. Composition of culture media, solutions and buffers is described. Overall, the classification of the process parameters and in-process controls and their acceptable ranges/acceptance criteria are adequately justified.

Reprocessing is only allowed in terms of re-filtration (only once per batch). The re-filtration operations are adequately described in the process description and supported by small-scale validation data. The small-scale validation is accepted and will be verified at manufacturing scale.

There are no intermediates defined for the active substance manufacturing process.

Control of materials

Raw materials and process materials used in the upstream and downstream process are listed together with their quality standard (in-house specification, compliant with Ph. Eur., USP, and/or NF), supplier (non-compendial materials), and their intended use. In addition to biological materials of plant or microbial origin, several animal derived materials are used in the cell culture process. Acceptable in-house specifications are

provided for the non-compendial raw materials. Active substance is fully formulated; the excipients (histidine, histidine hydrochloride monohydrate, trehalose, and water for injections) comply with Ph. Eur. requirements. In summary, the information provided on raw and process materials is considered sufficient.

The construction of the expression plasmid and its genetic elements are described in sufficient detail. In summary, the information on cell line development is satisfactory.

A two-tiered cell bank system with Master Cell Bank (MCB) and Working Cell Bank (WCB) has been established. The cell banking system is adequately described with sufficient details on manufacture and storage. Vials of both MCB and WCB are stored in separate locations. Satisfactory protocols describing manufacture and qualification acceptance criteria of new WCBs and routine stability monitoring of master and working cell banks are available.

The characterisation of the expression construct and cell substrate including MCB, WCB, EPCB, and Cells at LIVCA is in line with ICH Q5A, Q5B and Q5D. State-of-the-art analytical methods were applied.

Characterisation of the cell banks included tests for identity, purity in terms of potential microbial and viral contaminants (please refer to discussion under A.2 Adventitious agents safety evaluation), and genetic stability.

Control of critical steps and intermediates

In line with ICH Q8 and Q11, the applicant established a QTPP and identified, based on risk assessment, early development data, and product characterisation studies, putative CQAs of CT-P42 DP. The final CQAs of CT-P42 were determined from characterisation and similarity studies to the reference product and commercial scale manufacturing experience. A qualitative risk assessment is provided that considers potential direct or indirect effects of the CQA on biological activity, PK, efficacy, safety, and immunogenicity. Overall, the submitted risk assessment identifies the relevant attributes of aflibercept AS and FP and is deemed acceptable.

Sufficient descriptions of the analytical procedures/references to compendial methods for the CIPT and respective validation data have been provided.

Hold times are defined for seven in-process pools. The proposed hold times are supported by physicochemical and microbiological hold time data.

Process validation

In accordance with the Guideline on process validation for manufacture of biotechnology-derived active substances EMA/CHMP/BWP/187338/2014 the process validation activities for CT-P42 AS manufacture include process development/characterisation (see above), process verification studies, and continued process verification along the lifecycle.

Performance of the intended commercial AS manufacturing process was verified at the commercial manufacturing site Celltrion Plant I, Incheon, Republic of Korea, Single-use Plant (SUP). The extensive prospective process performance qualification (PPQ) encompassed manufacture of nine consecutive process validation batches at scale applying target operational set points and/or ranges on the bioreactor trains and the single purification train.

The operational ranges and acceptable ranges/acceptance criteria for process verification are justified by historical data from process development/characterisation and manufacturing. Upon completion of the process validation runs, CQAs as well as process parameters and in-process tests and their acceptance criteria were re-evaluated under consideration of additional knowledge from large scale manufacturing, and several

adjustments were implemented for commercial manufacturing. In the main, the adjustments are adequately justified by the applicant.

With a few exceptions, all process parameters (CPPs, non-CPPs) and process controls (CIPTs, IPTs, and IPMs) were within their acceptable ranges/acceptance criteria and consistent across the runs. The respective critical deviations and other major deviations are sufficiently described, and their impact has been adequately evaluated/justified. All validation batches met the AS release acceptance criteria applicable at time of validation and comply with the proposed commercial release acceptance criteria.

In summary, the presented process validation data demonstrate that the intended commercial AS manufacturing process performs consistently and delivers CT-P42 AS complying with the release specifications under commercial operating conditions.

Manufacturing process development

Throughout development different process versions were used to manufacture CT-P42 active substance.

Tables summarising the changes of the CT-P42 AS upstream and downstream process between the different process versions have been provided; the implemented changes are sufficiently justified.

An overview of the changes to specifications and analytical methods between the different process versions is presented. The changes to the methods and acceptance criteria are adequately described and justified.

Comparability of batches pre- and post-change between each version of the process used in development has been demonstrated considering sufficient number of batches and the approach for establishing comparability in each case is considered acceptable.

Characterisation

The applicant characterised the physicochemical and biological properties of CT-P42 using orthogonal, state-of-the-art analytical methods in line with the Guideline on development, production, characterisation and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008 and general Ph. Eur. monographs 0784. The analytical methods and their performance characteristics are sufficiently described.

Overall, results are consistent across AS batches and FP lots; the FP manufacturing process has only a minor impact on presence of HMWs and non-assembled forms/fragments.

Additional characterisation data (i.e. characterisation of charge variants, impact of glycosylation on biological activity, additional mechanism of action studies) are presented in Section 3.2.R.4:

Based on the results from forced degradation studies, HMW and LMW are classified as product-related impurities. Even for highly oxidised forms obtained by treatment with H_2O_2 no impact on biological activities was observed and hence, these forms can be classified as product-related substances.

As part of the extended characterisation studies, the impact of asialylation, amannosylation, agalactosylation, afucosylation, and aglycosylation on biological activity of CT-P42 was investigated.

An acceptable risk assessment on nitrosamine impurities has been provided. Considering the raw materials, manufacturing process and equipment as well as manufacturing environment the applicant´s conclusion that the risk for nitrosamine impurities is negligible can be agreed.

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

The commercial release specifications have been defined on the basis of process capability and product quality. The control tests proposed for the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, quantity, potency and safety (microbial).

The set of quality attributes tested at release of CT-P42 AS complies with ICH Q6B, Ph. Eur. general monograph 0784, and EMA/CHMP/BWP/532517/2008 and the proposed acceptance criteria are acceptable.

The release specification includes general compendial tests, compendial microbiological safety tests as well as in-house tests for identity, glycosylation, purity/impurity, potency assay, and content.

Analytical methods, validation of analytical methods

The analytical methods are satisfactorily described; unique method identifiers (in-house methods) or references to monographs (compendial methods) are provided. Key and reference materials as well as representative chromatograms and electropherograms are included. The implemented system suitability tests appear suitable to provide adequate control over analytical method performance. The capability of the stability indicating methods to detect product degradation/modification has been sufficiently demonstrated.

For all analytical methods used at release, the presented verifications and validation reports demonstrate suitability of the analytical procedures for their intended use. The relevant method performance characteristics have been assessed in accordance with ICH Q2(R1). Robustness of the analytical methods has been sufficiently demonstrated for a set of relevant variables. The validation experiments were primarily performed with the first preliminary RS and AS that were both manufactured using Process A (and stressed Process B-II AS samples for stability indicating methods).

Reference standards

For commercial testing the applicant implemented a two-tiered reference standard system.

The current primary reference standard (PRS) was derived from clinical AS batch that has been used to manufacture FP lot used in the comparative efficacy and safety study CT-P42 3.1. EU-approved Eylea. Acceptance criteria were based on those in the AS specification valid at time of testing. The proposed annual re-qualification programme is acceptable and expected to detect potential drifts.

Since initial submission, the working reference standard (WRS) has been established from AS batch and qualified against the current PRS in accordance with the previously submitted protocol.

The protocols for establishment and (re-)qualification of new PRS and WRSs are acceptable.

The information on the HCP assay reagents (antibody, HCP standard) is satisfactory. Comparative testing demonstrates that compared to the multi-product assay, the CT-P42 process-specific HCP ELISA has a higher sensitivity/specificity.

Batch analyses

Batch analyses data are presented for 31 AS batches. These include two 200 L batches manufactured according to Process A, three 1,000 L batches produced with Process B-I, and six 1,000 L batches manufactured using the clinical Process B-II. Batch data for twenty 1,000 L batches produced with the intended commercial Process C (11 batches of the initial failed PPQ and 9 of the PPQ). Except for the Process A batches (acceptance criteria for endotoxin, cIEF, non-red./red. CE-SDS, have been changed after release of these batches) all results comply

with the proposed commercial specifications. In summary, the presented results demonstrate that the manufacturing process reliably delivers CT-P42 AS with consistent quality.

Container closure system

The container closure system (CCS), i.e. pre-sterilised polycarbonate bottles with a cap coated with silicone liner and silicone tubing, is adequately described. Specifications, technical drawings, and representative release certificates are provided. The ready-to-use CCS is delivered gamma-sterilised (validation according to ANSI/AAMI/ISO 11137-2) by the vendor. The container meets the requirements of CFR 21, 177.2600 (rubber articles) and USP<381>, USP Class VI, 21 CFR section of the Food Additives Amendment of the Federal Food, Drug and Cosmetic Act, and is classified as non-cytotoxic material. The materials are not certified as being compliant with Ph. Eur. requirements. Suitability of the CCS is demonstrated by container closure integrity testing, results from stability studies, and a leachables assessment that included elemental impurities, volatile, semi-volatile, and non-volatile compounds.

2.3.2.4. Stability

Based on available real-time stability data the applicant proposes a shelf-life of 36 months for CT-P42 AS when stored in the CCS and protected from light.

Stability data are provided for long-term storage, intermediate, and accelerated conditions. In addition, data of a confirmatory photostability study are presented.

The design of the stability studies is in accordance with ICH Q5C. The samples are stored in containers that can be considered representative for the commercial CCS. Generally, the analytical programme follows the proposed AS release specifications and includes stability indicating methods.

Overall, the stability profiles of AS manufactured using previous variant of the process are comparable at all storage conditions further supporting the claim of comparability.

Confirmatory photostability study results were provided. It was concluded that CT-P42 AS should be stored protected from light.

In conclusion, based on the presented data the proposed shelf-life of 36 months in the container closure system when protected from light is approvable.

A commitment to complete the currently ongoing stability studies is provided. The applicant is reminded that in accordance with GMP requirements annual stability studies should be performed post-approval.

2.3.3. Finished Medicinal Product [Vial]

2.3.3.1. Description of the product and pharmaceutical development

CT-P42 finished product is a sterile liquid solution for intravitreal (IVT) administration, which is provided in both vial and pre-filled syringe. There are no differences in the formulation of finished product in Vial and PFS. Certain data from the PFS presentation has been used as supportive for the vial. The formulation of CT-P42 slightly differs from the RMP Eylea, the latter contains sodium phosphate.

The excipients are histidine, histidine hydrochloride monohydrate, sodium chloride, trehalose, polysorbate 20, and water for injections of compendial quality and controlled in compliance with tests and acceptance criteria of compendial monographs. There are no novel excipients, and no excipients of human or animal origin.

The sterile solution is filled aseptically into 3 mL (R2) Type I glass vials with rubber stoppers and flip-off seals. The CT-P42 vial-kit is a co-packaged combination product of the glass vial and an 18-gauge filter needle (5 µm) (Pack size: 1 vial and 1 filter needle/carton).

Each vial is designed to allow delivery of 2 mg of active ingredient in a 0.05 mL of solution at a nominal concentration of 40.0 mg/mL.

Container Closure System

The primary container closure system for CT-P42 finished product is composed of a 2R type I borosilicate glass vial, sealed with a 13 mm butyl rubber stopper and royal blue matte top button 13 mm flip off aluminium seal with a polypropylene disc. The stopper and vial both comply with Ph. Eur. and USP requirements.

One filter needle (5 µm) is supplied in the carton box for the withdrawal of the vial contents. The filter needle complies with applicable EU Directives / Regulation. The CE certification of the filter needle is provided. The CT-P42 vial finished product is packed in a paperboard box (1 vial/carton), to protect the vial and product from light and potential physical damage during handling, shipping, and storage.

CT-P42 finished product is intended for intravitreal (IVT) injection and no reconstitution is required for its administration. Prior to administration, CT-P42 finished product in a vial is withdrawn by the syringe via 5 µm filter needle and a 30-gauge injection needle is used for intravitreal administration. The 30-gauge injection needle and Luer lock syringe required for administration is not included in the CT-P42 vial packaging.

Compatibility of the primary container closure system with CT-P42 vial finished product over the proposed shelf life is being demonstrated. Compatibility of CT-P42 with the proposed commercial vial kit (filter needle) has been confirmed after withdrawal of all vial content into a syringe though the filter needle and incubation at room temperature for up to 30 minutes.

Microbiological safety of CT-P42 finished product vial is ensured by bioburden reduction filtration, sterile filtration, aseptic processing, aseptic filling into sterile vials and stoppering with sterile stopper, and by the integrity of the container closure system. Quality of excipients is controlled with in-house quality control test. Microbial safety of the finished product is controlled by in-process bioburden and endotoxin tests and release testing of active substance and finished product. Sterility of co-packaged device components in CT-P42 vial-kit is assured by the supplier.

Manufacturing process development

Manufacturing process development covers three different processes:

Key differences among the processes and history of the revision of release acceptance criterion are provided. All changes are properly justified.

A risk assessment regarding the risk of extractables from product contact materials during the FP manufacturing process has been provided, safety in terms of extractables has been confirmed.

2.3.3.2. Manufacture of the product and process controls

The name, address, and responsibility of the manufacturers are provided. A GMP compliance history is provided. GMP certificates are available in the dossier or in eudraGMP.

The manufacturing process of CT-P42 finished product consists of formulation of final bulk, bioburden reduction filtration, sterile filtration, aseptic filling, capping, and visual inspection processes. FP manufacturing starts after equilibration of AS at 2-8°C. The batch numbering system is explained.

The process control strategy is based on establishment of the quality target product profile (QTPP), identification of critical quality attributes (CQAs), risk assessment and establishment of the critical process parameters (CPPs) and definition of a control strategy to ensure that CT-P42 finished product consistently meets its QTPP. The CQAs determined for the active substance are also considered for the finished product. Additional CQAs such as appearance (colour and clarity), osmolality, pH, buffer components, protein content (concentration), sub-visible particle, visible particle, extractable volume and microbial purity) were identified for the finished product process, which are controlled during the finished product manufacture via process parameters, IPC and/or at release. There are no intermediates in the CT-P42 finished product manufacturing process.

Process validation

Process validation at Patheon was undertaken using 3 consecutive commercial scale CT-P42 vial finished product batches,

All process steps are properly validated and considered satisfactory.

Impurities

No additional impurities were detected in the CT-P42 finished product compared to the active substance based on the extensive physicochemical and biological test methods implemented.

A risk assessment has been conducted in compliance with ICH Q3D to assess the potential presence of elemental impurities in CT-P42 finished product considering the potential sources included in the manufacturing process. Two potential elements identified were detected at levels above the method quantification limit, but all detected elements present below permitted daily exposure (PDE) levels.

A risk assessment of nitrosamine impurities for CT-P42 Finished product was conducted to cover all raw materials (DS and primary packaging material), utility (water and nitrogen gas), Manufacturing Process of solution and product, equipment, master batch record and manufacturing Procedures and environment for Manufacturing and Storage. The risk evaluation of nitrosamines in CT-P42 Finished product is provided and confirm that there is no risk of presence of nitrosamines in CT-P42 Finished product.

2.3.3.3. Product specification, analytical procedures, batch analysis

Specification

Specifications were set considering ICH Q6B, EMA/CHMP/BWP/532517/2008 and Ph. Eur. monograph "Monoclonal Antibodies for Human Use" #2031, using release data or in-process data from CT-P42 vial and PFS finished product. Specifications are properly justified.

The Finished product release specification (vial) includes tests for general physical characteristics, identity, microbiological control, content, purity and potency.

Analytical procedures

Release and stability testing of CT-P42 vial finished product was done using compendial and non-compendial methods. Relevant pharmacopoeia references are provided for the compendial test methods. Since AS and FP have identical excipient composition and protein concentration, FP is analysed using the same assay procedures as used for AS and methods are cross referenced to the AS section. Method descriptions and method validation summaries have been updated to include the number of standard operating procedures (SOPs) for the non-compendial methods.

Batch results obtained with eleven CT-P42 vial finished product batches manufactured throughout development, indicating that the process is under control.

Since the CT-P42 finished product is equivalent to the active substance in its formulation, the reference standard used for control of CT-P42 active substance is also used for the control of CT-P42 finished product, which is endorsed.

2.3.3.4. Stability of the product

The stability program has been performed according to the guideline ICH Q5C. The stability strategy includes testing at long-term condition, accelerated condition, stress condition, a confirmatory photostability study and forced degradation studies.

Methods used for stability testing were validated prior the start of stability studies and are performed in the same manner as those performed during routine release test of the finished product.

The confirmatory Photostability Study show that CT-P42 finished product should be protected from light.

Comparable degradation profiles have been obtained by forced degradation studies.

Based on available stability data, the shelf life and storage conditions are acceptable. The shelf life for CT-P42 finished product vial is 24 months and, of 24 hours at out of fridge condition for CT-P42 finished product vial.

2.3.4. Finished Medicinal Product [PFS]

2 . 3 . 4 . 1 . Description of the product and Pharmaceutical Development

CT-P42 finished product is a sterile liquid solution for intravitreal (IVT) administration, which is provided in both vial and pre-filled syringe. There are no differences in the formulation of finished product in Vial and PFS. Certain data from the vial presentation has been used for as supportive for the PFS. The formulation of CT-P42 slightly differs from the RMP Eylea, the latter contains sodium phosphate.

The excipients are histidine, histidine hydrochloride monohydrate, sodium chloride, trehalose, polysorbate 20, and water for injections of compendial quality and controlled in compliance with tests and acceptance criteria of compendial monographs. There are no novel excipients, and no excipients of human or animal origin.

In the CT-P42 PFS, the sterile solution is filled aseptically into 0.5 mL cyclo olefin polymer (COP) syringes with chlorinated butyl rubber plunger stoppers and chlorinated butyl rubber luer lock tip caps with polypropylene outers.

Formulation development

No changes were made in the CT-P42 formulation during the manufacture of development batches, clinical batches and process performance qualification (PPQ) batches.

Characterization studies covering physicochemical and biological properties of aflibercept were conducted using active substance and finished product (PFS).

Container closure system

The primary container closure system for CT-P42 finished product is a 0.5 mL colourless, silicon oil-free and pre-filled cyclo olefin polymer (COP) syringe. The syringe barrel has an ink dose mark to allow delivery of 0.05 mL. The syringe is closed with a silicone resin bonded chlorinated butyl rubber plunger stopper and has a chlorinated butyl rubber luer lock tip cap with polypropylene outer. The syringe barrel has an ink dose mark to allow delivery of 0.05 mL. The COP syringe, plunger stopper, and tip cap meet both European Pharmacopoeia (Ph. Eur.) and United States Pharmacopoeia (USP) requirements. It is a common format for packaging of finished products intended for IVT administration. The 30-gauge injection needle required for administration is not included in the CT-P42 PFS packaging.

The CT-P42 PFS is an integral drug-device combination product. All device components suppliers operate under quality management system which complies with the requirements of EN ISO 13485:2016, and all PFS components are compliant to Iso standards.

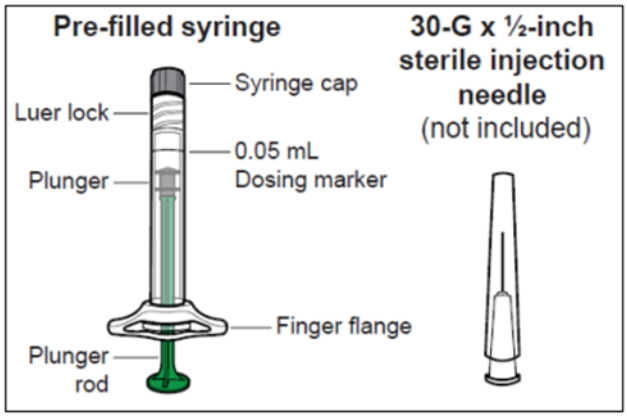


Figure 1: Scheme of CT-P42 pre-filled syringe as used in the instruction for use

The secondary container closure system for CT-P42 finished product PFS consists of a finger flange assembled onto the syringe body to improve syringe handling and injection administration, a plunger rod to support forces associated with drug delivery while maintaining finished product integrity and sterile barrier system (SBS) to maintain the sterility of the device. CT-P42 PFS finished product is packed in a paperboard box (1 syringe/carton) designed to protect the syringe and product from light and potential physical damage during handling, shipping, and storage.

Suitability of the PFS has been demonstrated by evaluation of several features of the container closure system.

CT-P42 PFS presentation is intended for intravitreal (IVT) injection and no reconstitution or dilution is required for its administration. During administration CT-P42 FP is in contact with the fluid pathway of the syringe and

the stopper, which are components of the primary container closure system. The 30-gauge injection needle required for administration is not included in the CT-P42 PFS packaging.

Medical device

All device components suppliers for PFS operate under quality management system which complies with the requirements of EN ISO 13485:2016. Compliance to standard requirements is confirmed for the syringe barrel (ISO 11040-6: 2019 and ISO 80369-7: 2021), plunger stopper (ISO 11040-5: 2012), biocompatibility tests (ISO 10993-1: 2018) and Break Loose and Gliding Force (BLGF) performance (ISO 11040-8: 2016).

In accordance with Article 117 of the Regulation (EU) 2017/745 on medical devices (the Medical Device Regulation, MDR), the conformity of the device part with the relevant General Safety and Performance Requirements (GSPRs) of CT-P42 PFS was submitted.

2.3.4.2. Manufacture of the product and process controls

Description of manufacturing process and process controls

The name, address, and responsibility of the manufacturers are provided. A GMP compliance history is provided. GMP certificates are provided in the dossier or available in eudraGMP. The document with Floor Plans of all facilities is available in the dossier.

Process validation

The manufacturing process of CT-P42 pre-filled syringe (PFS) finished product consists of bioburden reduction filtration of the DS, pooling, sterile filtration, aseptic filling and stoppering and visual inspection to produce the unassembled finished product (uDP). "Based on the provided data, it is indicated that the manufacturing process is capable of consistently product DP which meets the specifications"

2.3.4.3. Product specification, analytical procedures, batch analysis

The specifications have been generated taking into account guidance imparted in ICH Q6B Specifications, monographs of the European Pharmacopeia (EP), United States Pharmacopoeia (USP), Guideline EMEA/CHMP/BWP/532517/2008 and Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (FDA, 1997). In addition, as a combination product, ISO 11040-8 Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes was also taken into account to set the specification.

Specifications were set using release data or in-process data encompassing all historical manufacturing processes used during development and including lots used in clinical studies and/or stability studies, and validation batches. Release test is performed using unassembled finished product (uDP) sample except for sterility of syringe, which will be conducted using assembled and terminally sterilized finished product (aDP-TS).

The proposed release specifications for CT-P42 PFS finished product are identical to that of CT-P42 vial finished product except for the container closure system related items, Those specifications were set according to respective guidelines and monographs. Specifications are properly justified.

The Finished product release specification (PFS) includes tests for general physical characteristics, identity, microbiological control, content, purity and potency.

Release and stability testing of CT-P42PFS finished product was done using compendial and non-compendial methods. For non-compendial test methods, finished product is analysed using the same assay procedures as used for active substance, justified by the fact that AS and FP have identical excipient composition and protein concentration. A detailed description is provided additional analytical methods applied for stability testing. The applicant provided detailed validation report, including results, for the non-compendial method applied to CT-P42 PFS testing. The number of standard operating procedures (SOPs) have been included in the method descriptions and method validation summaries of non-compendial methods.

Since the CT-P42 finished product is equivalent to the active substance in its formulation, the reference standard used for control of CT-P42 active substance is also used for the control of CT-P42 finished product, which is endorsed.

2.3.4.4. Stability of the product

The proposed shelf life for CT-P42 finished product PFS is 24 months and of 24 hours at out of fridge condition for CT-P42 finished product PFS.

The stability program has been performed according to the guideline ICH Q5C. The stability strategy includes testing at long-term condition, accelerated condition, stress condition, and a confirmatory photostability study.

Methods used for stability testing were validated prior the start of stability studies and are performed in the same manner as those performed during routine release test of the finished product.

The confirmatory Photostability Study show that CT-P42 finished product should be protected from light.

Based on available stability data, the proposed shelf life for CT-P42 finished product is 24 months and 24 hours at out of fridge condition is acceptable.

2.3.4.5. Biosimilarity

Analytical similarity of CT-P42 was assessed in a comprehensive similarity exercise using EU-sourced Eylea as reference medicinal product (RMP). The analytical similarity assessment is well presented in the dossier per the relevant EU guidelines on the development of similar biological medicinal products (CHMP/437/04 Rev 1, EMA/CHMP/BWP/247713/2012), as well as the principles of comparability as per ICH Q5E. Figures and tables summarising the individual results and data distribution for each parameter, chromatographs, spectra, electropherograms etc. have been included. The approach and methodology of the analytical similarity assessment is sufficiently described and overall acceptable. The 2-way analysis included batches of EU-sourced Eylea, and batches of CT-P42. The CT-P42 and EU-approved Eylea lots were analysed in the analytical similarity studies. It is agreed that the batches used are well spread, covering different ages across the shelf life with sufficient overlap between both products.

The similarity ranges were established using data from analysis of EU-sourced Eylea batches. The approaches to compare physicochemical characteristics and biological quality attributes were described. The data is clearly presented no concerns were raised regarding the approaches used.

Two-way Similarity Assessment

The comprehensive set of orthogonal state-of-the–art analytical methods, which covers primary and higher order structure, post-translational modifications, size and charge variants, protein concentration, as well as

VEGF receptor domain- and Fc domain-related functions, is deemed adequate to address the relevant quality attributes of aflibercept. The descriptions and data for important method performance characteristics that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient and show suitability of the methods for the intended use. The attributes and analytical techniques used in the analytical similarity assessment are shown in Table 1.

For many quality attributes and particularly for the MoA related activities, CT-P42 was demonstrated to be analytically highly similar to EU-approved Eylea. Results from several analytical methods show differences between CT-P42 and EU-approved Eylea. These differences have been adequately evaluated by the applicant and are not expected to result in a different clinical performance of CT-P42.

In conclusion, the presented analytical data demonstrate analytical similarity of the proposed biosimilar CT-P42 and the reference product EU-approved Eylea. Minor analytical differences have been appropriately assessed by the applicant regarding their potential impact on clinical performance of the product. The observed differences are not expected to adversely impact clinical performance of CT-P42.

Table 1: Biosimilarity summary - comparing characterisation of CT-P42 versus Elyea

Category		Analytical Similarity Summary
Primary Structure	*Primary Amino Acid Sequence by Peptide Mapping (LC-MS)*	Identical
		Identical
		Identical
	Molecular weight by Deglyocsylated Intact Mass (LC-MS)	Similar
Post-Translational Modifications	*Deamidation*	Slightly lower level for CT-P42. No effect on safety or efficacy.
	Oxidation	Slightly lower level for CT-P42. No effect on safety or efficacy.
	C-terminal variants	CT-P42 had lower C-terminal lysine (Lys432). No effect on safety or efficacy.
Charge Variants	cIEF (pI)	Similar peak profile.
	cIEF (%Acidic group)	*Higher acidic level for CT-P42. No effect on efficacy or safety.*
	cIEF (%Main)	Similar
	cIEF (%Basic group)	Lower basic level for CT-P42. No effect on efficacy or safety.

Category		Analytical Similarity Summary
Glycation	Glycation	Slightly lower level for CT-P42 No impact on efficacy or safety.
Glycosylation	%Fucosylated group	Higher level for CT-P42. No effect on efficacy or safety.
	%Afucosylated group	Lower level for CT-P42. No effect on efficacy or safety.
	%Sialylated group	Lower level for CT-P42. No effect on efficacy or safety.
	%High mannose group	Higher level for CT-P42. No effect on efficacy or safety.
	Galactose molar ratio	Lower level for CT-P42. No effect on efficacy or safety.
	%Aglycosylation	Slightly higher for CT-P42. No effect on clinical impact.
Purity/Impurity	Aggregates by SEC-HPLC, SEC-MALS, AUC	Slightly higher level of monomer and lower level of HMW for CT-P42. No effect on biological activity or immunogenicity.
	Fragments by CE-SDS (Non-reduced, reduced)	Slightly higher purity and lower levels of fragments for CT-P42. No effect on biological activities.
Higher Order Structure	Free Thiol analysis	Similar
	Disulfide Bond	Similar
	FTIR,	Similar
	CD	Similar
	DSC	Similar
Content	Protein Concentration (SoloVPE)	Similar
VEGF Receptor Domain Binding	Anti-proliferation activity by VEGF-A165 binding	Similar
	Blockade activity of VEGF-A165 induced intracellular signals	Similar

Category		Analytical Similarity Summary
	VEGF-A165 binding	Similar
	VEGF-A121 binding	Similar
	VEGF-A110 binding	Similar
	VEGF-A189 binding	Similar
	VEGF-A206 binding	Similar
	VEGF-B167 binding	Similar
	VEGF-B186 binding	Similar
	PlGF-1 binding	Similar
	PlGF-2 binding	Similar
	Galectin-1 binding	Similar
Fc Binding	C1q binding	Similar
	FcγRIIIa-V Binding	Lower binding affinity for CT-P42. No effect on clinical impact
	FcγRIIIa-F Binding	Lower binding affinity for CT-P42. No effect on clinical impact
	FcγRIIIb Binding	Lower binding affinity for CT-P42. No effect on clinical impact
	FcγRIIa Binding	Similar
	FcγRIIb Binding	Similar
	FcγRI Binding	Similar

Category		Analytical Similarity Summary
	FcRn Binding	Similar

2.3.4.6. Adventitious agents

Multiple complementary 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 microbiological 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 (filtration of media and buffers, low bioburden process, microbial reduction filtrations, sterile filtration, aseptic processing) and adequate sanitisation procedures.

Animal-derived materials

TSE certificates of suitability or certificates of origin are available. Based on the information provided, it is agreed that the risk with regard to TSE is negligible. Considering the origin, processing, and testing of the animal-derived materials, the risk for contaminating viruses is low and mitigated by testing of cell banks and bulk harvest, and virus clearance by the process.

Microbial agents

MCB, WCB, and EPCB were tested for the absence of bacterial, fungal, and mycoplasma contamination. Absence of mycoplasma is also confirmed by testing of the unprocessed bulk material. Bioburden and endotoxin tests are performed on media and buffers and multiple stages of the AS and FP manufacturing processes. At the release stage, AS and FP are tested for bioburden/sterility as well as endotoxin content.

Adventitious viruses

Absence of viruses in MCB, WCB, and EPCB was determined by a battery of tests covering a broad range of potentially contaminating viruses.

Unprocessed bulk has been tested for the absence of adventitious viruses. Unprocessed bulks used for commercial production are routinely tested.

Virus clearance studies

The virus clearance capacity of the manufacturing process has been assessed in virus clearance studies using small-scale models of the respective large-scale manufacturing steps. The design of the studies is in line with the guidance documents ICH Q5A and CPMP/BWP/268/95. Validity of the down-scaled models has been sufficiently confirmed; a tabular comparison of the small-scale and the manufacturing scale process has been provided. The original study reports have been provided.

In conclusion, the two dedicated virus clearance steps in combination with the affinity and mixed mode chromatography steps provide for an effective and robust overall clearance capacity for enveloped and non-enveloped adventitious viruses.

In summary, the risk of potential contamination and transmission of bacterial, viral, or TSE agents is considered to be acceptably low.

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

Active substance

Eydenzelt (CT-P42) is a presented as a biosimilar to the reference product Eylea. CT-P42 active substance is manufactured using a typical manufacturing process for monoclonal antibodies and Fc fusion proteins. Its active substance aflibercept, a recombinant human fusion protein combining immunoglobulin (Ig) domain 2 of human VEGFR-1 with Ig domain 3 of human VEGFR-2 and the constant region of human IgG1, is expressed in a CHO cell line, and subsequently purified by three column chromatography steps (affinity, cation exchange, and multimodal anion exchange chromatography) and ultra/diafiltration. Two dedicated virus clearance steps are implemented in the active substance manufacturing process. The manufacturing process including the process parameters and in-process controls as well as potential re-processing have been described in sufficient detail. Manufacturing authorisations and/or GMP certificates are available for all active substance manufacturers.

Raw materials and process materials used in the upstream and downstream process are listed together with their quality standard (in-house specification, compliant with Ph. Eur., USP, and/or NF), supplier (non-compendial materials), and their intended use. The excipients comply with Ph. Eur. requirements. Some animal-derived components are used in the cell culture process. Overall, the information provided on raw and process materials is considered sufficient**.**

The expression system and cell banks are described adequately. A protocol for implementation of new WCBs is available.

The overall control strategy was established in accordance with ICH Q11 using an enhanced development approach and ensures that material of sufficiently high quality will be released to the market. The relevant critical quality attributes of CT-P42 have been determined using risk assessment tools and linked to the individual process steps. The applicant sufficiently characterized the CT-P42 process, product variants using orthogonal state-of-the-art analytical methods and degradation pathways. Batch analyses data show high consistency across the active substance batches.

Hold times of process intermediate pools are justified by chemical and microbiological hold time data.

Removal of process-related impurities, residual raw materials and leachables to acceptable low levels has been demonstrated by small-scale studies and confirmed at scale or is sufficiently justified. Based on risk assessment the risk for nitrosamine impurities is negligible.

The shipping process of active substance to the CT-P42 finished product manufacturers has been appropriately validated. Comparability of process changes for the active substance manufacturing process as well as changes to the specifications and analytical methods are sufficiently described and justified.

The proposed active substance release and stability specifications are acceptable. The descriptions of the analytical methods applied for release testing of active substance are sufficiently detailed and validated in accordance with ICH Q2.

The preliminary and primary reference standards used throughout development are sufficiently described and characterised.

Active substance is stored in gamma-irradiated polycarbonate bottles with a cap assembled with silicone tubes and lined by silicone. The container closure system is sufficiently described. The container materials comply with applicable CFR 21 and USP Class VI requirements and are classified as non-cytotoxic. Compliance with Ph. Eur. requirements is not certified but leachables studies are being performed. No elements or compounds above the analytical evaluation threshold have been detected so far. The final study report for the ongoing leachables study will be submitted**.**

A shelf-life of 36 months at -75 ± 15°C for CT-P42 AS when stored in the CCS described under 3.2.S.6. and protected from light is proposed by the applicant. Based on the submitted data the claimed shelf-life is approvable.

Finished product

CT-P42 finished product is a sterile liquid solution for intravitreal (IVT) administration which is provided in a single-use vial or pre-filled syringe. No reconstitution or dilution is required for its administration.

There are no differences on the formulation of finished product in vial and PFS: the CT-P42 active substance (40.0 mg/mL) is mixed with formulation buffer (histidine, sodium chloride, trehalose, polysorbate 20, pH 6.2). The excipients are of compendial quality and controlled in compliance with tests and acceptance criteria of compendial monographs. There are no novel excipients, and no excipients of human or animal origin. Formulation development studies were conducted first in vial and subsequently also in PFS. The chosen formulation is supported by the studies performed**.** The formulation of CT-P42 slightly differs from the RMP Eylea.

Finished product vial-kit

The CT-P42 vial-kit is a co-packaged combination product. The kit includes a 3 mL (2R) type I borosilicate glass vial (sealed with rubber stopper and a polypropylene disc) and an 18-gauge filter needle (5 µm). (Pack size: 1 vial and 1 filter needle/carton). The stopper and vial both comply with Ph. Eur. and USP requirements, and the filter needle complies with applicable EU Directives / Regulation. The CE certification of the filter needle has been provided. The 30-gauge x ½-inch injection needle and luer lock syringe required for administration is not included.

A target fill volume is set to ensure the delivery of a single dose of 0.05 mL containing 2 mg aflibercept.

Compatibility of the primary container closure system with CT-P42 vial finished product over the proposed shelf life has been demonstrated. The applicant committed to submit the final study report of the leachable studies**.**

Manufacturing development covers three different processes: Comparability among the FP manufactured with the three processes has been confirmed. Changes among the processes have been properly justified**.** The risk assessment regarding the risk of extractables from product contact materials during the FP manufacturing process confirmed safety in terms of extractables.

The manufacturing process is supported by process characterization and validation data.

The overall control strategy was established based on the quality target product profile (QTPP), identification of critical quality attributes (CQAs), risk assessment and establishment of the critical process parameters (CPPs) and definition of a control strategy to ensure that CT-P42 finished product consistently meets its QTPP Batch analyses results demonstrate that the control strategy is adequate and appropriately validated and that the process can reproducibly produce finished product of expected quality. Microbiological safety of CT-P42 finished product vial is appropriately assured.

Impurities in the CT-P42 finished product were equivalent to those of the active substance. A risk assessment for nitrosamine formation confirmed that there is no risk of presence of nitrosamines in CT-P42 Finished product.

Specifications were set considering ICH Q6B, EMA/CHMP/BWP/532517/2008 and Ph. Eur. monograph "Monoclonal Antibodies for Human Use" #2031, using release data or in-process data from a total 17 batches of CT-P42 vial and PFS finished product, encompassing all historical manufacturing processes used during development. Specifications are properly justified and methods validated.

Since the CT-P42 finished product is equivalent to the active substance in its formulation, the reference standard used for control of CT-P42 active substance is also used for the control of CT-P42 finished product (vial and PFS), which is endorsed.

Stability studies have been conducted on CT-P42 vial finished product according to ICH Q5C. Polysorbate degradation rate will be controlled at AS level. The shelf-life of CT-P42 vial finished product stored at 5 ± 3°C is 24 months, as claimed in the SmPC.

Finished product PFS

The CT-P42 PFS is an integral drug-device combination product: 0.5 mL cyclo olefin polymer (COP) syringe with rubber plunger stopper (Pack size: 1 syringe/carton). The 30-gauge x ½-inch injection needle required for administration is not included.

A target fill volume is set to ensure the delivery of a single dose of 0.05 mL containing 2 mg aflibercept.

Compatibility of FP with the designated syringe and stopper has been addressed during long-term stability studies. Product protection was confirmed by confirmatory photostability studies and container closure integrity testing. Leachable studies on terminally sterilized CT-P42 PFS samples (aDP-TS confirm the compatibility of CT-P42 PFS finished product with syringe and stopper. No leachables have been detected from the available 9 months data point, The applicant committed to provide the final study report of the leachable studies on CT-P42 PFS (aDP-TS)**.**

Microbiological safety of CT-P42 finished product PFS is ensured by bioburden reduction filtration, sterile filtration, aseptic processing, aseptic filling into sterile PFS and stoppering with sterile stopper. The sterility of finished product is ensured and verified via container closure integrity testing and Microbial safety of CT-P42 finished product PFS is controlled by in-process bioburden and endotoxin tests, and by sterility, endotoxin, sterility of the syringe at FP release.

Manufacturing development covers three different processes Results of the three comparability studies confirm that CT-P42 vial finished product and PFS finished product are considered comparable in all quality attributes and in physicochemical and biological characteristics, and that the different processes utilized for PFS (and vial) manufacturing at different sites, have no impact on CT-P42 finished product quality.

The manufacturing process is supported by process characterization and validation data. The overall control strategy has been adequately described and validation of unit operations, component sterilization and aseptic processing has been demonstrated.

Impurities in the CT-P42 finished product were equivalent to those of the active substance. A risk assessment for nitrosamine formation confirmed that there is no risk of presence of nitrosamines in CT-P42 Finished product.

Specifications have been generated taking into account relevant guidance documents. In addition, as a combination product, ISO 11040-8 Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes was also taken into account to set the specification. Specifications were set using release data or in-process data from a total 17 batches of CT-P42 vial and PFS finished product. Reference standard used for control of CT-P42 active substance is endorsed The proposed finished product PFS release and stability specifications are supported. The methods are properly validated, and detailed validation reports have been provided for the non-compendial method applied to CT-P42 PFS testing.

Stability studies have been conducted on CT-P42 PFS finished product according to ICH Q5C. The proposed shelf-life of CT-P42 PFS finished product stored at 5 ± 3°C for 24 months is supported by the real-time data provided.

Medical device - PFS

All device components suppliers for PFS operate under quality management system which complies with the requirements of EN ISO 13485:2016. Biocompatibility testing has been performed and is acceptable. A usability study risk assessment has been performed, and it is concluded that human factor study for CT-P42 PFS is not necessary. The notified body opinion has been submitted.

Biosimilarity

The applicant performed a sound and comprehensive analytical biosimilarity exercise with CT-P42 and EU-approved Eylea finished product in vial and in PFS lots included.

The relevant quality attributes of the aflibercept molecule were assessed using a broad panel of orthogonal standard and state-of-the-art techniques. Analysis covered primary sequence and higher order structure, protein concentration, analysis of glycosylation and other post-translational modifications, as well as charge and size heterogeneity. 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 main analytical similarity study is complemented by additional mechanism of action studies, a detailed characterisation of charge variants, and studies investigating the impact of glycosylation on biological activities. These complementary studies are adequately designed to support the conclusions drawn. In addition, results of comparative forced degradation studies including two lots each of both presentations are presented.

For many quality attributes including those related to the MoA, analytical similarity between CT-P42 and the reference product EU-approved Eylea was demonstrated. Minor analytical differences observed in the level of deamidation, oxidation, C-terminal Lysine, isoaspartate, distribution of charge variants, glycation, glycoform distribution, aglycosylation, content of HMW variants, free thiols, and FcγRI, FcγRIIb, and FcγRIIIa/b binding have been adequately evaluated and justified. It is agreed that an impact on clinical performance is not expected. Results of the studies on charge variants and the impact of glycosylation support the conclusion on similarity. Similar degradation profiles and kinetics were determined for CT-P42 and the reference product under thermal, oxidative, UV-light, and low/high pH stress further supporting biosimilarity.

In summary, from a quality perspective it is concluded that CT-P42 is similar to EU-approved Eylea.

Appendices

The information on facilities and major equipment including GMP status is mainly satisfactory. The document with floor plans of all facilities is available in the dossier.

Adventitious agents

The risk of contamination and for transmission of adventitious agents is adequately controlled and minimised by complementary measures implemented at various stages of the manufacturing process.

Conclusion

From the quality perspective CT-P42 has been demonstrated to be analytically similar to the RMP EU-approved Eylea and is considered approvable as proposed biosimilar to Eylea. An update of the dossier is requested with the closing sequence: the paragraph „Active substance Blending Justification" in Section 3.2.P.3.5.1.1.1 uDP [PFS] has to be deleted.

In conclusion, based on the review of the quality data provided, it is considered that the marketing authorisation application for Eydenzelt (CT-p42) is approvable from the quality point of view.

2.3.6. Recommendation(s) for future quality development

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

2.4. Non-clinical aspects

2.4.1. Introduction

Analytical and functional similarity between CT-P42 and EU-approved Eylea was demonstrated in *in vitro* studies. No additional non-clinical pharmacodynamics studies, neither *in vitro* nor *in vivo*, were performed.

2.4.2. Pharmacology

The applicant submitted a 2-way similarity assessment, evaluating biological similarity of CT-P42 and EU-approved Eylea in regard to potency and functional activities, by conducting following assays: binding to VEGF-A165, VEGF-A121, VEGF-A110, VEGF-A189, VEGF-A206, VEGF-B167, VEGF-B186, PlGF-1, PlGF-2 (all by ELISA), Galectin-1 (by SPR), cell-based hVEGF blockade activity assay, anti-proliferation assay using HUVECs, binding to C1q (by ELISA), FcRn and FcγR binding affinities (by SPR).

Additional characterization studies for EU-approved Eylea and CT-P42 (e.g.: binding affinities and kinetics of VEGF-A isoforms, VEGF-B and PlGF forms by surface plasmon resonance (SPR), the prove of non-binding to VEGF-C and VEGF-D as well as the lack of ADCC and CDC activities) were further performed.

Overall, the *in vitro* biosimilarity exercise seems to be appropriate. For a thorough assessment of all *in vitro* PD studies, please refer to the discussion and conclusion in the Quality section.

No *in vivo* animal studies were conducted in addition to the analytical biosimilarity assessment of CT-P42 and its referenced medicinal product Eylea, sourced from EU.

No dedicated safety pharmacology studies were conducted with CT-P42 drug product, whereas safety pharmacology endpoints as clinical observations, electrocardiography and heart rate were investigated within the scope of the 12-week repeat-dose toxicity study in cynomolgus monkeys. No concerns were identified.

2.4.3. Pharmacokinetics

Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies were performed with CT-P42 and Eylea.

Aflibercept (CT-P42 or Eylea concentrations in plasma and vitreous humour were determined for the toxicokinetic similarity assessment incorporated in the comparative 12-week repeat-dose toxicity study in cynomolgus monkeys.

Therefore, the applicant submitted a GLP-compliant method validation report for the determination of free CT-P42 and Eylea in cynomolgus monkey K2 EDTA plasma and a non-GLP compliant method qualification report for the determination of free CT-P42 and Eylea in cynomolgus monkey vitreous humour, both using an Electrochemiluminescence assay (ECL). Typical validation characteristics, as calibration curve performance and comparability, precision and accuracy, dilutional linearity and hook effect, selectivity, and stability and robustness, were determined.

For plasma samples, the method had a lower limit of quantification (LLOQ) of 25.00 ng/mL and an upper limit of quantification (ULOQ) of 1000.00 ng/mL, whereas for vitreous humour the assay range was 10 (LLOQ) to 500 ng/mL (ULOQ).

All method performance parameters met the method validation or qualification acceptance criteria.

In the comparative toxicokinetic assessment of CT-P42 and Eylea cynomolgus monkeys (3/sex/group) received intravitreal administrations of CT-P42 or Eylea at 2 mg/eye (4 mg) or vehicle control once every 4 weeks on day 1, 29 and 57. Aflibercept (CT-P42 or Eylea concentrations in plasma and vitreous humour were determined pre- and up to 672 hours post-dose.

In plasma, CT-P42 and Eylea concentrations were similar with test article comparison ratio values (CT-P42/Eylea) ranging from 0.905 to 1.14 for C_{max} and from 0.954 to 1.09 for AUC_{0-672} (C_{max} of CT-P42 for males and females combined at day 1: 6.16µg/mL and at day 57: 4.58µg/ml; C_{max} of Eylea for males and females combined at day 1: 5.41µg/mL and at day 57: 5.07µg/ml), with no obvious differences in sex, neither accumulation of aflibercept after multiple dosing nor reduction in exposure due to possible anti-drug antibody (ADA) development. For CT-P42, a median T_{max} of 24 hours was observed on day 1 and of 72 hours on day 57, whereas a mean half-life ($t_{1/2}$) of 117 hours was reached on day 1 and of 125 hours on day 57. For Eylea, a median T_{max} of 72 hours was observed on day 1 and day 57, whereas a mean half-life ($t_{1/2}$) of 84.4 hours was reached on day 1 and of 114 hours on day 57.

In vitreous humour, mean left and right vitreous humour combined concentration values of CT-P42 and Eylea were comparable, with obvious differences in sex within the same treatment groups (CT-P42: 5400 ± 6070 ng/mL for males and 1210 ± 1330 ng/mL for females at day 57; Eylea: 3970 ± 2210 ng/mL for males and 1390 ± 1110 ng/mL for females at day 57). After 672 hours post-dose at day 57, mean, for males and females combined, concentration ratios of vitreous humour to plasma of 22.1 ± 22.4 for CT-P42 and 46.1 ± 21.6 for Eylea were observed.

2.4.4. Toxicology

Although animal *in vivo* studies are generally not required for a biosimilar within the EU under the assumption that physiochemical and functional similarity between the test product and the RMP can be proven first and foremost in the *in vitro* biosimilarity exercise and, as such, were not endorsed by the EMA in a previous scientific advice (EMA/CHMP/SAWP/78691/2020), the applicant conducted a comparative 12-week repeat dose toxicity study in cynomolgus monkeys with CT-P42 and US-licensed Eylea including toxicokinetic analysis to fulfil global requirements.

2.4.4.1. Repeat dose toxicity

To compare the toxicity profiles of CT-P42 and US-licensed Eylea, cynomolgus monkeys (3/sex/group) received intravitreal administrations of CT-P42 or Eylea at 2 mg/eye (total of 4 mg) or vehicle control once every 4 weeks on day 1, 29 and 57.

Animals were monitored regarding mortality, clinical observations, body weights, qualitative food consumption, blood pressure, electrocardiography (ECG), ophthalmic observations, intraocular pressure (IOP), full-field electroretinography (ffERG), clinical pathology (haematology, coagulation, clinical chemistry and urinalysis), toxicokinetics and anatomic pathology (macroscopic observations, organ weight, and microscopic observations).

A mild to moderate anterior segment inflammatory response 2 days postdose was noted in animals treated with CT-P42 and EU-approved Eylea, with no loss of visual function (assessed by ERG and VEP) and a slightly less ophthalmic inflammation in the CT-P42 test article group. A no observed adverse effect level (NOAEL) was determined with 2mg/eye for CT-P42, since findings for CT-P42 and EU-approved Eylea were regarded as comparable and non-adverse.

2.4.5. Ecotoxicity/environmental risk assessment

In the case of products containing proteins as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) should be provided, whereby this ERA may consist of a justification for not submitting ERA studies, e.g. that due to the nature of particular pharmaceuticals they are unlikely to result in a significant risk to the environment (EMEA/CHMP/SWP/4447/00 corr 2 issued 01 June 2006).

The applicant provided a valid justification for the absence of ERA studies with Eydenzelt,

2.4.6. Discussion on non-clinical aspects

Generally, according to 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 Rev1, Dec 2014), a stepwise approach is recommended for evaluation of the similarity of the biosimilar and the reference product, since *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, and therefore these *in vitro* assays can be considered as paramount for the non-clinical biosimilar comparability exercise.

Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity are not required for non-clinical testing of biosimilars, which usually applies for studies on local tolerance as well.

Scientific advice was provided to the applicant in February 2020 (EMA/CHMP/SAWP/78691/2020), supporting this approach to not conduct non-clinical *in vivo* studies. However, a comparative 12-week repeat-dose toxicity study in cynomolgus monkeys including TK assessment was performed with CT-P42 and Eylea to fulfil global requirements, providing supplemental information about the investigational drug.

Pharmacology

A thorough *in vitro* biosimilar comparability exercise, primarily based on a series of *in vitro* functional and binding assays, was conducted with CT-P42 drug product and its comparator Eylea sourced from EU. The complete package was forwarded and therefore assessed throughout the Quality section. The package is deemed adequate, and the results support the biosimilarity.

No pharmacodynamic *in vivo* animal studies were conducted in addition to the analytical biosimilarity assessment, which is accepted.

No dedicated safety pharmacology studies were conducted with CT-P42 drug product, whereas safety pharmacology endpoints as clinical observations, electrocardiography and heart rate were investigated within the scope of the 12-week repeat-dose toxicity study in cynomolgus monkeys.

Pharmacokinetics

Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies were performed with CT-P42 and Eylea.

A comparative toxicokinetic assessment of CT-P42 and Eylea after intravitreal administration was included in the 12-week repeat-dose toxicity study in cynomolgus monkeys, where aflibercept (CT-P42 or Eylea) concentrations were determined pre- and up to 672 hours post-dose in plasma and vitreous humour samples. Therefore, a validated electrochemiluminescence (ECL) assay and a qualified ECL assay were used to determine the plasma or vitreous humour concentrations of CT-P42 and Eylea, respectively. All method performance parameters, as calibration curve performance and comparability, precision and accuracy, dilutional linearity and hook effect, selectivity, and stability and robustness, met the method validation or qualification acceptance criteria. The PK analysis showed a similar plasmatic distribution profile for both products. However, for both CT-P42 and Eylea, the vitreous humour concentrations (measured at 672h post day 57 dose) showed a great variability, with differences of almost 13-fold (e.g. for CT-P42, vitreous humour concentration ranged from 532 to 7000 ng/mL). This variability becomes a major difference in the ratio vitreous humour to plasma concentrations (22.1 ± 22.4 for CT-P42 and 46.1 ± 21.6 for Eylea). Given the lack of toxicity and that no related concern arises from the clinical studies, it could be understood that this difference is due to the variability in a single time point of measurement rather than the biosimilar product actually presenting a different distribution pattern. Thus, this finding is deemed of no clinical significance. No other concern arises from the PK analysis, whose results support the biosimilarity.

Toxicology

A comparative 12-week repeat dose toxicity study was conducted in cynomolgus monkeys with CT-P42 and US-licensed Eylea. The clinical dose of 2mg Aflibercept and the intravitreal route of administration were used to reflect the clinical situation. No relevant toxicity was observed in this in vivo study. Mild differences in the electroretinography parameters were observed, but the lack of concordance between the findings and their small magnitude led the applicant to consider them of no clinical significance. A no observed adverse effect

level (NOAEL) was determined to be 2mg/eye for CT-P42, since findings for CT-P42 and US-licensed Eylea (e.g. ophthalmic inflammation) were regarded as comparable and non-adverse.

Neither single dose toxicity, genotoxicity, carcinogenicity, developmental and reproductive toxicology, local tolerance nor other toxicity studies were performed with CT-P42, which was considered acceptable.

Environmental risk

Aflibercept is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

Therefore Eydenzelt (aflibercept by Celltrion Healthcare) is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

Not applicable.

2.4.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, no concern was identified which would argue against a marketing authorisation application. Overall, the non-clinical development is deemed adequate, and the results support the biosimilarity.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

- **Tabular overview of clinical studies**

Table 2: Overview of CT-P42 clinical development programme

Study	Design	Objectives and Endpoints	Treatment	Status
CT-P42 3.1 (Comparative efficacy and safety study)	Phase 3, double-masked, randomized, active controlled, parallel group study to compare efficacy and safety of CT-P42 and EU-approved Eylea in patients with DME	**Primary:** To demonstrate that CT-P42 was similar to EU-approved Eylea in terms of efficacy as determined by clinical response according to the mean change from baseline in BCVA using the ETDRS chart at Week 8 **Secondary:** To evaluate additional efficacy, PK, usability (vial kit and PFS), and overall safety including immunogenicity	**Main Study Period (Double-masked, active controlled):** 2 mg/0.05 mL of CT-P42 or EU-approved Eylea IVT injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses up to Week 52 · **Randomized: 348** - CT-P42: 173 - EU-approved Eylea: 175 **Extension Study Period (Open-label, single-arm)[1]:** 2 mg/0.05 mL of CT-P42 IVT injection via a single-dose PFS at Extension Week 0 · **CT-P42: 31**	**Completed** (CSR CT-P42 3.1)

[1] After the completion of Main Study Period, a total of 31 patients from Main Study Period, regardless of the treatment group in Main Study Period, were enrolled in a 4-week open-label, single-arm extension study to evaluate the usability, efficacy and safety of CT-P42.
Abbreviations: BCVA, best corrected visual acuity; CSR, clinical study report; DME, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study

2.5.2. Clinical pharmacology

A separate clinical Phase 1 PK study was not conducted, since it was considered not meaningful to determine the biosimilarity based on the low level of aflibercept in serum following IVT administration.

The clinical phase 3 study provided supportive PK data (plasma concentration following 1st and 5th IVT injections) in accordance with the EMA guideline and FDA guidance: Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1), FDA guidance Clinical pharmacology data to support a demonstration of biosimilarity to a reference product (FDA, 2016).

No specific studies dedicated to human PD have been performed for aflibercept and the PD data was derived from in vitro, animal, and human efficacy studies (Eylea EPAR, 2012). No validated PD markers considered relevant to predicting efficacy of aflibercept in DME patients are known. Therefore, no PD markers were included in the clinical study with CT-P42.

2.5.2.1. Pharmacokinetics

Bioequivalence

Study CT-P42 3.1

Design and methods of the study are described in detail in the Section on Clinical Efficacy.

PK sampling and data analysis

Pharmacokinetic (PK) samples were obtained during Main Study Period of Study CT-P42 3.1, where patients were administered either 2 mg/0.05 mL CT-P42 or EU-approved Eylea IVT injection using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses.

According to the statistical analysis plan (SAP), PK data were to be summarized on PK set. Also, all plasma concentrations data and PK parameters were to be listed for all patients in Safety set for Main Study Period who agreed to the collection of PK blood samples.

The PK Set was defined as patients who received at least one full dose of study drug and had at least one post-treatment PK concentration data in Main Study Period. Following that PK evaluation was conducted in a subgroup of patients, it was considered as a stratification factor to resolve imbalance between subgroups.

Blood samples for assessment of C_{max1}, C_{max2}, T_{max1}, and T_{max2} of free (VEGF-unbound) study drug concentrations in plasma were to be collected at predose within 60 minutes, 24 ± 2 hours, 48 ± 2 hours, and 72 ± 6 hours after the first and the fifth study drug administration, respectively, in approximately 40 patients (20 patients per treatment group).

For plasma concentrations summary, the following rules applied:

- Below lower limit of quantification (BLQ) was to be treated as zero (0) for calculation of all descriptive statistics except for geometric means. For the calculation of geometric means, BLQ values were to be set to 0.5 * lower limit of quantification (LLoQ).
- No further imputation was to be applied to any missing values.

Descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for plasma concentrations were to be presented by treatment group at each scheduled visit and time point. Geometric mean was to be only calculated if at least 2/3 of all plasma concentration values were valid and higher than LLoQ for respective time point. Also, the proportion of patients with plasma concentration higher than LLoQ was to be summarized using frequency tables by each visit and time point period.

Results

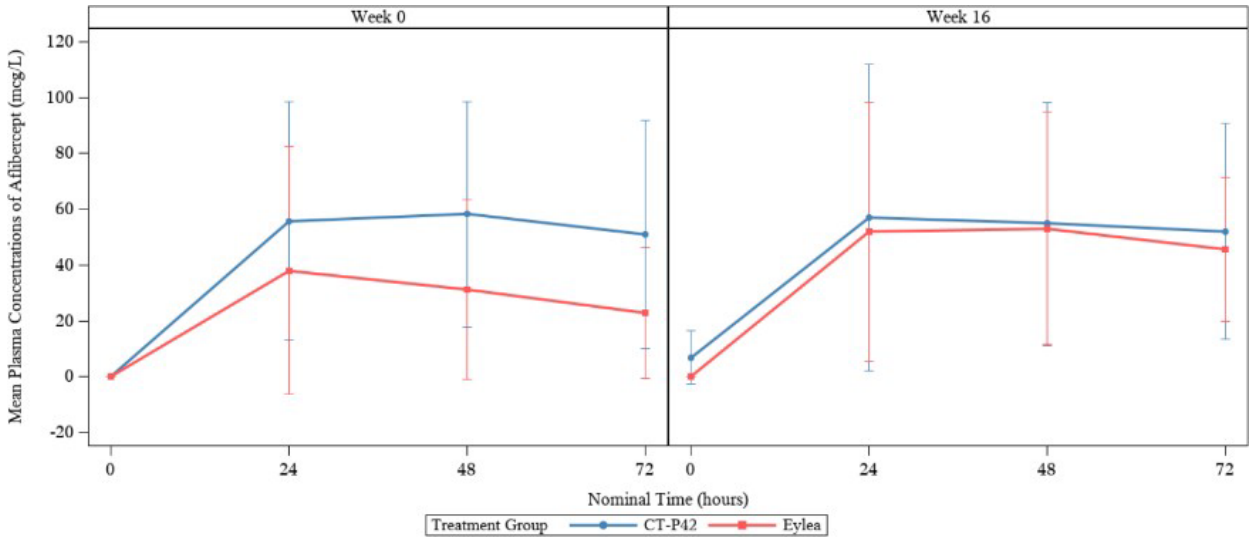
Of the 348 patients (173 and 175 patients in the CT-P42 and EU-approved Eylea groups, respectively) randomized, 23 (6.6%) patients (11 [6.4%] and 12 [6.9%] patients in the CT-P42 and EU-approved Eylea groups, respectively) were included in the PK Set.

According to the applicant, the baseline characteristics and the demographic characteristics of the patients in the PK Set were comparable between the CT-P42 and EU-approved Eylea groups.

The plasma concentrations of aflibercept in the PK Set are illustrated by treatment group in the following figure. The observed plasma concentrations were generally similar between the treatment groups, though the data should be interpreted with caution considering the small number of the PK Set and high variability. Furthermore,

the data indicated that the accumulation of free aflibercept after repeated administration was not observed in both treatment groups.

Figure 2: Mean ± SD plasma concentration of aflibercept by treatment and visit in study CT-P42 3.1 (PK set)



The PK parameters (C_{max1}, C_{max2}, T_{max1}, and T_{max2}) of aflibercept are summarized by treatment group in the following table. Overall, the PK parameters were generally similar between the 2 treatment groups with the mean ± SD ranges widely overlapping for each of the PK parameters.

Table 3: Plasma pharmacokinetic parameters of aflibercept in study CT-P42 3.1 (PK set)

Parameter Statistic	CT-P42 (N=11)	EU-approved Eylea (N=12)
C_{max1} (mcg/L)		
n	11	11
Mean ± SD	66.79 ± 42.70	42.93 ± 43.64
Geometric Mean	53.46	30.95
CV%	63.9	101.7
Median (Min, Max)	66.70 (0.0, 153.0)	34.40 (0.0, 156.0)
C_{max2} (mcg/L)		
n	8	10
Mean ± SD	64.41 ± 52.49	57.12 ± 46.51
Geometric Mean	49.90	41.56
CV%	81.5	81.4
Median (Min, Max)	53.20 (0.0, 183.0)	58.70 (0.0, 157.0)
T_{max1} (h)		

n	11	11
Mean ± SD	40.7152 ± 22.0180	36.9227 ± 16.3752
Geometric Mean	35.7819	33.9879
CV%	54.1	44.3
Median (Min, Max)	24.0000 (22.333, 72.333)	25.0667 (22.833, 71.667)
T_{max2} (h)		
n	8	10
Mean ± SD	43.9833 ± 23.9879	42.6700 ± 22.4691
Geometric Mean	38.2631	37.5524
CV%	54.5	52.7
Median (Min, Max)	35.0833 (21.667, 71.417)	35.6417 (22.433, 72.833)

Note: If C_{max1} or C_{max2} is zero (0), 0.5 * LLoQ (LLoQ = 16 mcg/L) was used for the calculation of geometric means. Abbreviations: C_{max1}, maximum plasma concentration after 1st study drug administration; C_{max2}, maximum plasma concentration after 5th study drug administration; CV%, percent of coefficient of variation; LLoQ, lower limit of quantification; Max, maximum; Min, minimum; n, the number of patients; SD, standard deviation; T_{max1}, time of observed C_{max1}; T_{max2}, time of observed C_{max2}

2.5.2.2. Pharmacodynamics

Mechanism of action

Aflibercept exerts its therapeutic effects by binding to Vascular Endothelial Growth Factor A (VEGF-A) and placental growth factor (PlGF) thereby inhibiting the binding and activation of these cognate VEGF receptors. VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; Vascular Endothelial Growth Factor Receptor 1 (VEGFR-1) and Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2), present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and excessive vascular permeability.

Aflibercept acts as a soluble protein decoy for VEGFRs (VEGFR-1 and VEGFR-2) present on the surface of endothelial cells in the retina. Aflibercept preferentially binds to VEGF-A and PlGF with a much greater affinity than its natural angiogenic competitors (VEGFR-1 and VEGFR-2). Through this mechanism, aflibercept prevents ligand-induced dimerization of VEGFR-2, preventing downstream activation of the intracellular tyrosine kinase domains from inhibiting pathologic angiogenesis. Aflibercept exerts its inhibitory effects on VEGFRs preventing endothelial proliferation, vascular permeability, and neovascularization.

Based on the totality of the published literature and in line with prior CHMP reviews of Eylea, the binding to VEGF-A and PlGF is considered to be the principal MoA of aflibercept for all the indications for which Eylea is approved.

Primary and secondary pharmacology

Not applicable.

Immunological events

Immunogenicity was evaluated based on the Safety Set for Main Study Period (from Week 0 through Week 52 or the first end of study visit [EOS1]), defined as all randomly assigned patients who received at least 1 dose (full or partial) of either study drug in Main Study Period for CT-P42 3.1, and all subjects in the Safety Set for Main Study Period were analysed according to the treatment they actually received.

The subjects were considered as post-treatment ADA or NAb positive if they had at least 1 "Positive" ADA or NAb result after drug exposure. Post-treatment ADA and NAb status was determined regardless of the results at pre-dose. The immunogenicity sample at baseline was taken prior to the first administration of study drug, so the results at baseline were excluded in the analysis of post-treatment ADA and NAb status.

The proportions of patients with positive ADA or NAb results by each visit and the proportion of patients who had at least 1 post-treatment ADA or NAb positive results are presented below. The proportion of patients with post-treatment ADA or NAb incidences was low for both CT-P42 and EU-approved Eylea groups and similar between the treatment groups. No notable differences were observed between the 2 treatment groups.

Table 4: Frequency of ADA and NAb in study CT-P42 3.1 (safety set for main study period)

Visit **ADA** **Result** **NAb** **Result**	**CT-P42 (N=174)**	**EU-approved Eylea (N=174)**
	Number (%) of patients	
Week 0 (Pre-dose)		
ADA Positive	3 (1.7%)	2 (1.1%)
NAb Positive	0	0
Week 8 (Pre-dose)		
ADA Positive	3 (1.7%)	2 (1.1%)
NAb Positive	2 (1.1%)	0
Week 16 (Pre-dose)		
ADA Positive	2 (1.1%)	1 (0.6%)
NAb Positive	0	1 (0.6%)
Week 24 (Pre-dose)		
ADA Positive	2 (1.1%)	2 (1.1%)
NAb Positive	0	0
EOS1*		
ADA Positive	1 (0.6%)	2 (1.1%)
NAb Positive	0	2 (1.1%)

Post-treatment (up to Week 52 pre-dose)		
At Least One Positive ADA[1]	3 (1.7%)	4 (2.3%)
At Least One Positive NAb[2]	2 (1.1%)	2 (1.1%)

Abbreviation: EOS1, the first End of Study visit; N, The number of patients in the Safety Set for Main Study Period
Note: The ADA test involved both screening and confirmatory assays to confirm true positive results. Samples that were potentially positive in the screening assay were spiked with excess study drug to determine if patients were a true positive, labelled as 'Positive'. The NAb screening assessments were only made on samples with an ADA confirmatory assay result of 'Positive'.
* The EOS1 visit occurred at Week 52, 4 weeks after the last dose at Week 48. Patients who discontinued early from the study visited the study centre at least 4 weeks after the last dose of the study drug, or at Week 8 in case of patients who discontinued the study drug before the completion of Week 8 for EOS1 evaluations.
[1] At least one ADA positive result after the first study drug administration, regardless of ADA status at pre-dose visit includes all scheduled and unscheduled visits during the Main Study Period.
[2] At least one NAb positive result after the first study drug administration.

To estimate the magnitude of ADA positive response, ADA titre results were summarized. The mean and the median ADA titre results were generally similar between the 2 treatment groups at each visit except for EOS1 where relatively higher titre was observed in the EU-approved Eylea group because of 1 patient in the treatment group with exceptionally high titre of 450. The number of ADA positive patients is small (1 patient and 2 patients in the CT-P42 and EU-approved Eylea group, respectively), so interpretation of the results should be done with caution. All patients with ADA positive results showed low ADA titre, except for the one patient mentioned above.

Impact of ADA on PK

None of the patients in the PK Set had positive ADA results, the impact of immunogenicity on PK could not be assessed.

Impact of ADA on Efficacy

The impact of ADA on efficacy was assessed in Study CT-P42 3.1. The mean change from baseline in best corrected visual acuity (BCVA) using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart at Week 8 was also descriptively analysed by ADA status for the Full Analysis Set (FAS).

Table 5: Descriptive statistics for change from baseline of BCVA at week 8 by ADA status in study CT-P42 3.1 (FAS)

Subgroup Statistic	CT-P42 (N=173)		EU-approved Eylea (N=175)	
	ADA positive	ADA negative	ADA positive	ADA negative
n	3	164	2	164
Mean ± SD	10.7 ± 11.0	8.6 ± 6.2	14.5 ± 0.7	7.8 ± 6.3
Median	10.0	8.0	14.5	7.0
Min, Max	0, 22	-7, 27	14, 15	-18, 25

Note: Patients who showed at least one "Positive" result in immunogenicity test obtained after study drug exposure up to Week 8 were considered as "ADA positive subgroup" regardless of ADA status at pre-dose assessment. All patients

who had only “Negative” results obtained after study drug exposure up to Week 8 were considered as “ADA negative subgroup”.

Based on the ADA subgroup analysis, the mean change from baseline in BCVA scores at Week 8 was greater in the ADA positive subgroups compared to the ADA negative subgroups for both CT-P42 and EU-approved Eylea groups. However, due to low ADA incidences (< 2%) and high SD values, this does not allow meaningful comparison of efficacy results between the ADA positive and negative subgroups. Since aflibercept is intended for IVT administration to exert local effects in the eye, ADA positivity is not expected to have any clinically relevant impact on the efficacy of CT-P42.

Impact of ADA on safety

Out of 7 patients in total (3 and 4 patients in the CT-P42 and Eylea groups, respectively) reported as at least one ADA positive after study drug administration, 4 patients (2 patients in each of the treatment groups) experienced at least 1 treatment-emergent adverse event (TEAE) and there was no study drug related TEAE. In addition, there were no patients who experienced treatment-emergent serious adverse event (TESAE) or TEAE leading to study drug discontinuation. As the number of ADA positive patients was very limited, the impact of immunogenicity on safety could not be assessed.

2.5.3. Discussion on clinical pharmacology

Analytical methods

PK assay

A single assay approach was chosen for determination of aflibercept in samples drawn from study subjects treated with CT-P42 or EU-approved Eylea. The concentration of aflibercept in CTAD plasma samples was determined with a sandwich assay on the MSD-ECL platform which is well described in the dossier. The quantification range of the method is 16 to 1024 ng aflibercept/mL. The method has been validated in accordance with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) that was effective at time of validation and testing. Based on the provided information the method was considered adequately validated and suitable for its intended use. Assay performance during clinical sample analysis was comparable to its performance during assay validation.

Determination of ADA

Method ICDIM 531 and method ICDIM 532 were developed to measure anti-aflibercept antibodies (ADA) and neutralizing anti-aflibercept antibodies (NAbs). In general, method validation was in accordance with the state of the art and considered acceptable.

Drug tolerance was also assessed during the validation of method ICDIM 532. Results obtained suggest that NAb determination could be influenced by aflibercept levels. For this procedure, no further comments arise as only a few patients were ADA positive, but this information should be taken into account for future procedures in which this method could be used.

Overall, sample analysis to quantify aflibercept concentrations and to determine ADA and NAbs was carried out in accordance with EMA Guidelines and the state of the art.

Pharmacokinetics

A separate clinical phase 1 PK study was not conducted based on the low level of aflibercept in serum following IVT administration. Basing comparability on such scenario is regarded futile and thus not meaningful. Thus, as agreed with EMA during the scientific advice procedures, PK samples were obtained during Main Study Period of Study CT-P42 3.1, where patients were administered either 2 mg/0.05 mL CT-P42 or EU-approved Eylea IVT injection using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses.

Maximum concentration (C_{max}) and time to maximum concentration (T_{max}) of free (VEGF-unbound) study drug concentrations in plasma were assessed as secondary PK endpoints at pre-dose as well as 24 hours, 48 hours and 72 hours after both the 1st and the 5th study drug administration.

Objective and endpoints including descriptive evaluation of the comparative PK assessment have been agreed with the applicant during the scientific advice procedures and considered acceptable.

However, the number of patients included in the PK Set was distinctly lower than initially planned. It was also noted that PK results were not available for all the patients in the PK Set at all time points.

It was originally planned to include 20 patients per arm in the PK subset of the pivotal clinical trial as agreed during the scientific advice procedures. However, besides the challenges posed by frequent study centre visits for patients with decreased visual acuity, the COVID-19 pandemic and the war in Ukraine posed additional obstacles to the recruitment of patients for the PK subset. Thus, the sample size for the PK subset was re-evaluated and it was concluded to recruit 12 patients per arm. This reduced sample size was supported by an evaluation of the precision of the estimates for geometric mean ratio at various sample sizes. Of those 24 patients, 11 patients in the CT-P42 group and 12 patients in Eylea group were included in the PK analysis. One patient in CT-P42 group was excluded, as the PK samples were not delivered to the central laboratory due to war in Ukraine.

As expected, the observed systemic aflibercept concentrations in patients' plasma were generally low (mean C_{max} approximately 42 to 68 ng/mL) and comparable with known data for the reference product (mean C_{max} values of free aflibercept in plasma in the range of 30 to 50 ng/mL).

At Week 0 (24h-72h after IVT injection), plasma concentration of aflibercept was somewhat higher in the CT-P42 group (mean 66.79 ± 42.70 mcg/L) compared to the Eylea group (mean 42.93 ± 43.64 mcg/L). At Week 16 (24h-72h after IVT injection), mean aflibercept plasma levels were 64.41 ± 52.49 in the CT-P42 group and 57.12 ± 46.51 in the Eylea group. Large variation was observed for the PK measurements (CV for mean C_{max} values ranging from 63.9% to 101.7%), which can be explained by the large variability of these estimated due to the limited number of subjects in the PK Set and especially the overall low levels of free drug concentration in plasma.

Comparable values were obtained for the time of maximum plasma concentration between products with T_{max} values ranging from approximately 22 to 72 hours, however, also with a high degree of variation.

Despite the large degree of variation between samples, the reported PK data demonstrate that the systemic drug concentrations of test and reference product were in the same range, comparable to historic control data, distinctly below levels required to exert a pharmacologic effect, and there was no evidence of accumulation after repeated dosing.

Moreover, according to the study report, IVT aflibercept was allowed for the fellow eye treatment during the whole study period. However, the MAH has clarified that only 6 patients included in the PK substudy received aflibercept treatment in the fellow eye between week 1 and week 12 and that for every patient, predose

concentrations were BLQ at week 16. Consequently, it seems that aflibercept administration in the fellow eye does not influence PK analysis.

Pharmacodynamics

No dedicated comparative pharmacodynamics (PD) investigations have been performed as part of the clinical biosimilarity exercise. This was considered acceptable for this biosimilar application considering the information available regarding the reference product.

Immunological events

Immunogenicity assessment was conducted as part of study CT-P42 3.1. Blood samples for immunogenicity assessment were collected prior to study drug administration (pre-dose) at Week 0 (Day 1), Week 8, Week 16, Week 24, and Week 52 (the first End-of-Study visit), or when immune-related adverse events occurred. This approach followed Scientific Advice and is endorsed. The 348 subjects of the safety set were included in the immunogenicity assessment. At baseline comparable proportions of patients were positive for pre-existing ADAs: 3/174 (1.7%) of subjects in the CT-P42 group and 2/174 (1.1%) in the Eylea group.

Throughout the study duration the proportion of ADA and NAb positive subjects was low in both groups. The proportion of patients who had at least one ADA positive result after the study drug administration (up to Week 52) was similar between the CT-P42 and the Eylea groups (1.7% and 2.3%, respectively). The proportion of patients who had at least one NAb positive result after drug exposure was the same in both treatment groups (1.1%). All the detected ADAs in both treatment groups were generally of low titre over the study period, except for 1 patient in the Eylea treatment group, with exceptionally high titre of 450.

None of the patients in the PK Set had positive ADA results. Thus, the impact of immunogenicity on PK could not be assessed. The impact of ADA on efficacy was assessed in Study CT-P42 3.1. Based on the ADA subgroup analysis, the mean change from baseline in BCVA scores at Week 8 was greater in the ADA positive subgroups (CT-P42: 10.7 ± 11.0; Eylea: 14.5 ± 0.7) compared to the ADA negative subgroups (CT-P42: 8.6 ± 6.2; Eylea: 7.8 ± 6.3). However, due to low ADA incidences (< 2%) and high SD values, a meaningful comparison of efficacy results between the ADA positive and negative subgroups cannot be made.

With regard to the impact of immunogenicity on safety, the overall incidence of TEAEs in ADA positive patients was higher in the CT-P42 group [2/3 (66.7%)] compared to the Eylea group [2/4 (50.0%)]. This imbalance can hardly be interpreted due to the overall low number of ADA positive patients and should be viewed in conjunction with the overall safety profile and the totality of evidence. Of note, none of the TEAE in the ADA positive patients was considered study drug related or serious or led to study drug discontinuation. In addition, none of the subjects with post-treatment ADA positive results experienced any TEAEs consistent with a potential immune response, such as intraocular inflammation.

2.5.4. Conclusions on clinical pharmacology

Similarity between both treatments was assessed evaluating plasma concentrations at week 0 and week 16. The reported PK data demonstrated that the systemic drug concentrations of test and reference product were in the same range, comparable to historic control data, distinctly below levels required to exert a pharmacologic effect, and there was no evidence of accumulation after repeated dosing.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

Not applicable.

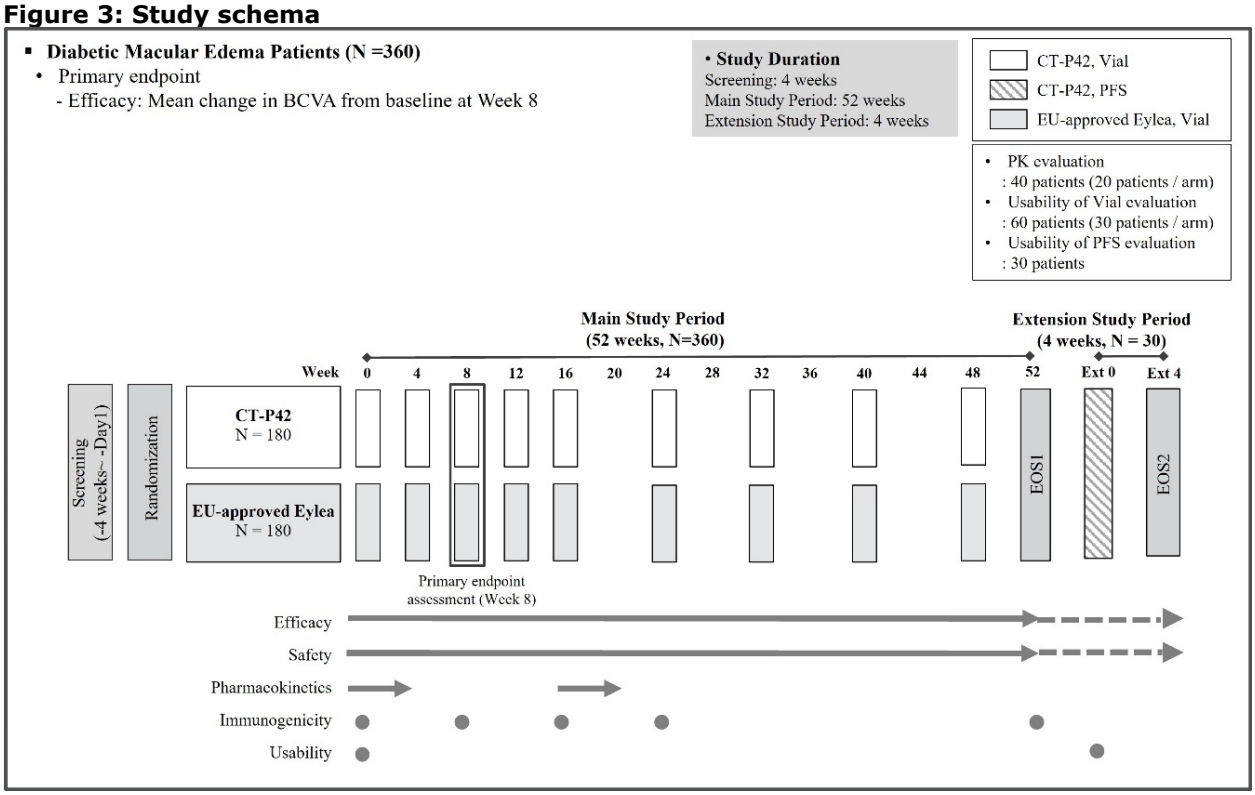
2.5.5.2. Main study(ies)

Title of study

Study CT-P42 3.1

This was a randomized, active-controlled, double-masked, parallel-group, and multicentre Phase 3 study designed to evaluate the efficacy, PK, usability, and overall safety including immunogenicity of CT-P42 compared with EU Eylea via IVT injection using a single dose vial kit followed by a 4-week open-label, single-arm extension study to evaluate the usability, efficacy and safety of CT-P42 via IVT injection using a PFS in patients with DME.

Figure 3: Study schema



Schematic outline. Abbreviations: BCVA, best corrected visual acuity; EOS, End-of-Study; Ext 0, Extension Week 0; Ext 4, Extension Week 4

Methods

During the Main Study Period (52 weeks), subjects were randomized and administered either 2 mg/0.05 mL CT-P42 or EU-approved Eylea IVT injection (in a 1:1 ratio) using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses. After the completion of Main Study Period, a total of 31 patients (15 and 16 patients in the CT-P42 and EU-approved Eylea groups, respectively) received one additional dose of CT-P42 via IVT injection using a single-dose PFS at Extension Week 0 regardless of the treatment group in Main Study Period.

On Day 1 (Week 0), patients who met all of the inclusion criteria and none of the exclusion criteria were enrolled in the study. For patients who met criteria in both eyes, the eye with the worst best corrected visual acuity (BCVA) was selected as the study eye. Only 1 eye per patient could be the 'study eye'. If a patient had DME with similar BCVA in both eyes, the eye with the clearest media was selected as the study eye. If the ocular media of both eyes were similar in clarity, the patient's non-dominant eye (if identifiable) was selected as the study eye. If neither eye is dominant, the right eye was designated as the study eye. Eligible patients were randomly assigned to either the CT-P42 or EU Eylea group in a 1:1 ratio. The randomization to treatment assignment was stratified as follows: BCVA score (< 55 letters versus ≥ 55 letters) using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart on Day 1, country and PK subgroup (Yes versus No). For patients who discontinued the study drug prior to the completion of Week 8 visit, the patients were asked to return to the site at Week 8 to complete all planned assessments for the Week 52/EOS1 visit.

482 patients were screened, of which 348 were enrolled and randomly assigned to study drug for Main Study Period (173 and 175 patients in the CT-P42 and EU-approved Eylea respectively). A total of 31 patients were enrolled in Extension Study Period (15 and 16 patients in the CT-P42 and EU-approved Eylea groups, respectively in Main Study Period).

- **Study Participants**

The patient population consisted of adult male and female patients aged ≥ 18 years with DME secondary to DM type 1 or 2 involving the centre of the macula in the study eye. Eligible patients had to have central subfield retinal thickness of ≥ 350 µm as assessed by OCT and BCVA score of 73 to 34 (approximate Snellen equivalent of 20/40 to 20/200) using ETDRS charts in the study eye.

The study was to be conducted in 83 centres in 13 countries (Czech republic, Estonia, Germany, Hungary, India, Latvia, Lithuania, Poland, Republic of Korea, Russian Federation, Slovakia, Spain, Ukraine), but eventually no patients were recruited in Germany.

Main Inclusion criteria:

1. Male or female patient aged ≥ 18 years.
2. Patient who has type 1 or 2 DM.
3. Patient with DME secondary to DM involving the centre of the macula (defined as the OCT central subfield) in the study eye.
4. Patient whose central subfield retinal thickness is ≥ 350 µm as assessed by OCT based on central results in the study eye at Screening.

5. Patient who has BCVA score of 73 to 34 (approximate Snellen equivalent of 20/40 to 20/200) using ETDRS charts in the study eye at Screening and Day 1 (for more detailed BCVA procedures, see the study procedure manual).
6. Decrease in vision determined to be primarily the result of DME in the study eye.

Main Exclusion Criteria

1. Patient who has only one functional eye, even if the eye met all other study requirements, or has and/or is likely to have amblyopia, amaurosis or ocular disorder with BCVA < 34 ETDRS letter score (approximate Snellen equivalent of < 20/200) in the fellow eye.
2. Patient who currently has, or has a history (where indicated) of ocular condition including one or more of the following in the study eye:
    a) Active proliferative DR, or pre-retinal fibrosis involving the macula
    b) Aphakia
    c) Vitreomacular traction or epiretinal membrane that is expected to affect central vision
    d) Iris neovascularization, vitreous haemorrhage, or tractional retinal detachment
    e) Ocular inflammation (including trace or above)
    f) Uncontrolled glaucoma or filtration surgery for glaucoma in the past or likely to be needed in the future
    g) Intraocular pressure ≥ 25 mmHg
    h) Spherical equivalent of the refractive error of worse than -6 dioptres myopia
    i) Structural damage to the centre of the macula that is likely to preclude improvement in BCVA following the resolution of macular oedema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates
    j) Concurrent and/or history of disease, other than DME, that could compromise VA, require 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) as assessed by the investigator
    k) Inability to obtain fundus and OCT images due to, but not limited to, insufficient media clarity or inadequate pupil dilation
3. Patient who currently has, or has a history (where indicated) of ocular condition including one or more of the following in either eye:
    a) Concurrent and/or history of idiopathic or autoimmune uveitis
    b) Evidence or suspicion of infection including blepharitis, keratitis, scleritis, or conjunctivitis. However, a patient who has completely recovered from the infection at Day 1 is allowed to be enrolled at the investigator's discretion.
4. Patient who currently has, or has a history of (where indicated) systemic condition including one or more of the following:

a) Uncontrolled DM as defined by HbA1c > 10%

b) Uncontrolled blood pressure (BP) defined as systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg measured after 5 minutes of rest while sitting

c) History of vascular disease such as cerebrovascular accident, myocardial infarction, transient ischemic attack, or thromboembolic reaction including pulmonary embolism within 180 days prior to the first study drug administration

d) New York Heart Association Functional Classification Class III or IV heart failure, or severe uncontrolled cardiac disease (i.e., unstable angina)

e) Current treatment for serious systemic infection

f) History of recurrent significant infections in the opinion of the investigator

g) Renal failure requiring dialysis or renal transplant

h) History of malignancies within 5 years prior to the first study drug administration, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ

i) History of other disease, metabolic dysfunction, physical examination finding, ECG finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that, in the opinion of the investigator, contraindicates the use of the study drug or that might affect interpretation of the study results or render the patient at high risk for treatment complications

j) Evidence of significant uncontrolled concomitant diseases including cardiovascular system, nervous system, pulmonary, renal, hepatic, endocrine, gastrointestinal disorders, or psychiatric condition as assessed by the investigator

5. Patient who has one or more previous/concomitant treatments of the following:

a) Previous systemic or ocular treatment with aflibercept including potential biosimilars

b) Previous treatment with ocular anti-angiogenic agents (e.g., pegaptanib sodium, bevacizumab, ranibizumab) in the study eye

c) Administration of systemic anti-angiogenic agents and/or ocular anti-angiogenic agents in fellow (non-study) eye within 180 days prior to the first study drug administration

d) Previous use of intraocular or periocular corticosteroids including dexamethasone implant (e.g., Ozurdex) within 180 days, or fluocinolone acetonide implant (e.g., Iluvien) within 36 months prior to the first study drug administration in the study eye

e) Laser photocoagulation (panretinal or macular) in the study eye within 90 days prior to the first study drug administration

f) More than two previous macular laser treatments, and/or focal laser scars in the fovea that could limit BCVA improvement in the study eye

g) History of vitreoretinal surgery including scleral bucking in the study eye

h) Any intraocular surgery including cataract surgery in the study eye within 90 days prior to the first study drug administration or planned or expected during the study

i) Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days prior to the first study drug administration

j) Treatment with any investigational medicinal product and/or device within 30 days or 5 half-lives, whichever is longer, prior to the first study drug administration

Treatments

Dose, dosing interval and duration of the intervention for CT-P42 was based on the efficacy and safety data for Eylea in the DME population, based on Eylea's phase 3 studies VIVID^{DME} and VISTA^{DME}.

Figure 4: Schedule of study assessments

	Screening	Main Study Period											Extension Study Period	
Dose		**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**EOS1[1]**	**10**	**EOS2**
Study visit (Week)	**-4**	**0**	**1**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**Ext 0**	**Ext 4**
Study visit (Day)	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**169**	**225**	**281**	**337**	**365**	**1**	**29**
Visit window (days)[2]	-	-	-1 to +2	±7									-	±7
Screening/Baseline														
Informed consent	X												X[3]	
Demographics, medical/ophthalmic history	X													
NYHA Functional Classification	X	X										X		
Weight	X											X		X
Physical examination	X											X		X
12-lead ECG[4]	X											X		X
Inclusion and exclusion criteria	X	X[5]												
Randomization[6]		X												
Pre-injection assessments														
Pregnancy test[7]	X	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[8]	X	X			X			X		X[9]		X		X
Pharmacokinetic sampling[10]		X					X							
Immunogenicity sampling[11]		X			X		X	X				X		
Pre-injection ophthalmologic assessments														
Best corrected visual acuity (ETDRS chart)[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP test[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optical coherence tomography[13, 14]	X	X#	X#	X#	X#	X#	X#	X#	X#	X#	X#	X#		
FP[13]	X	X#			X#			X#				X#		
FA[13]	X[15]											X#		
Study drug administration														
Study drug administration (CT-P42 or Eylea)		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#,16	
Hypersensitivity monitoring[17]		X		X	X	X	X	X	X	X	X		X	

	Screening	Main Study Period											Extension Study Period	
Dose		**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**EOS1[1]**	**10**	**EOS2**
Study visit (Week)	**-4**	**0**	**1**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**Ext 0**	**Ext 4**
Study visit (Day)	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**169**	**225**	**281**	**337**	**365**	**1**	**29**
Visit window (days)[2]	-	-	-1 to +2	±7									-	±7
Post-injection ophthalmologic assessments														
Finger count, hand motion, light perception[18]		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#	
Indirect ophthalmoscopy[19]		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#	
IOP test[19]		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#	
Other assessments														
Injection task assessment (usability)[20]		X											X	
Prior/concomitant treatments[21]	X												X	
AEs monitoring[22]	X												X	

Abbreviations: AE, adverse event; BP, blood pressure; DME, diabetic macular edema; ECG, electrocardiogram; EOS, end-of-study; EOS1, the first end-of-study; EOS2, the second end-of-study; ETDRS, Early Treatment of Diabetic Retinopathy Study; Ext 0, Extension Week 0; Ext 4, Extension Week 4; FA, fluorescein angiography; FP, fundus photography; HbA1c, hemoglobin A1c; ICF, informed consent form; IOP, intraocular pressure; NYHA, New York Heart Association; OCT, optical coherence tomography; PFS, prefilled syringe; SD-OCT, spectral-domain optical coherence tomography.

Notes: The ophthalmologic assessments marked as "X#" were performed only for study eye. If not specified, the ophthalmologic assessments were performed for both eyes throughout the study.

1. The assessments in EOS1 were performed at Week 52 for all patients who completed the Main Study Period. Patients who discontinued early from the study visited the study center at least 4 weeks after the last dose of the study drug administration for EOS1 evaluations. For patients who discontinued the study drug before the completion of the Week 8 visit, the patients were asked to return to the site at Week 8 to complete all planned assessments for the EOS1 visit.
2. A visit window of -1 to +2 day(s) was allowed at Week 1 and a visit window of ±7 days was allowed thereafter up to the last EOS visit based on the first study drug administration date. If any study visit had to be rescheduled, subsequent visits had to follow the original visit date and allowed window.
3. Patients participating in the Extension Study Period signed the ICF before participation in the Extension Study Period.
4. All scheduled 12-lead ECGs were performed locally after the patient had rested quietly for at least 5 minutes in the supine position. If patients had signs and symptoms of hypersensitivity or other cardiac origin, additional ECGs could be performed at any time during the whole study period. Regardless of the ECG result, further cardiological evaluation could be done at the investigator's discretion.
5. The inclusion and exclusion criteria were needed to be confirmed by screening results before the randomization on Day 1.
6. The randomization was performed before the first study drug administration (Day 1).
7. For women of childbearing potential, serum pregnancy test was conducted at Screening and analyzed at the central laboratory. Only patients with a negative serum pregnancy test result were enrolled in the study. For women of childbearing potential, a urine pregnancy test was used to confirm patients were not pregnant before the dosing on each scheduled visit or more frequently if required by country-specific legislation. Urine pregnancy test was performed locally. If a urine pregnancy test result was positive or equivocal, a confirmatory serum pregnancy test was performed at the local laboratory.
8. Clinical laboratory tests were carried out as scheduled. Hematology included red blood cells count, total and differential white blood cell count, absolute lymphocytes count, absolute neutrophils count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, and HbA1c. Clinical chemistry included total protein, total serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, creatine kinase, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, C-reactive protein, and uric acid. Urinalysis included color, bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination. Clinical laboratory test samples were analyzed at the central laboratory.
9. At Week 40, only HbA1c was assessed.
10. Pharmacokinetic blood samples for the determination of plasma concentration of study drug were planned to be collected in approximately 40 patients (20 patients per treatment group). Pharmacokinetic sampling could be performed on an in-house stay basis upon the investigator's discretion. The sampling schedule was as follows.

Study Visit	Sampling Time point	Window
First dose (Week 0, Day 1) /Fifth dose (Week 16, Day 113)	Predose	within 60 minutes
	24 hours after study drug administration	± 2 hours
	48 hours after study drug administration	± 2 hours
	72 hours after study drug administration	± 6 hours

11. Samples for immunogenicity testing were collected before the dosing of the study drug. Additional immunogenicity was assessed when immune-related AEs occurred.
12. Assessment was performed before the pupil dilation.
13. Assessment was performed after the pupil dilation.
14. The same device of SD-OCT was used throughout the study. Image acquisition with another OCT device was discussed and approved by the central image center before being used. If a switch was inevitable, the switched machine type was used for the remainder of the study.
15. For Screening, FA images which were obtained within 4 weeks before the first study drug administration could be used as screening data if the FA images were acquired by qualified photographers according to the procedures described in the study procedure manual.
16. Patients could receive treatment with CT-P42 PFS. CT-P42 PFS on Extension Week 0 was recommended to be administered 8 weeks after the last study drug administration in the Main Study Period (Week 48). However, the actual dosing interval from the last administration of study drug in the Main Study Period (Week 48) could be determined based on investigator's discretion.
17. Additional vital signs including BP, heart and respiratory rates, and body temperature were monitored within 1 hour after the study drug administration for possible hypersensitivity reactions. Hypersensitivity was also monitored by patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation had to be available and any types of ECG could be performed, if indicated.
18. Assessment was performed within 15 minutes after the study drug administration.
19. Assessment was performed within 60 minutes after the study drug administration.
20. Tasks specific to the unpacking, preparing, proper administration and disposal of the study drug by healthcare professionals were assessed by the study center personnel.
21. The use of all prior and concomitant treatments for DME, from the diagnosis of disease to the last EOS visit, was recorded. The use of all medications for other purposes, taken from 30 days before the first administration of the study drug until the last EOS visit, was recorded. For eligibility check, relevant medication history was also recorded.
22. AEs were assessed from the date the ICF was signed until the last EOS visit, regardless of the relationship to the study drug. AEs of special interest were closely monitored. After the last EOS visit, serious adverse drug reactions were reported to the Sponsor or its designee.

During Main Study Period, patients were administered either 2 mg/0.05 mL CT-P42 or EU-approved Eylea IVT injection (in a 1:1 ratio) using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses. After the completion of Main Study Period, a total of 31 patients received one additional dose of CT-P42 via IVT injection using a single-dose PFS at Extension Week 0 regardless of the treatment group in Main Study Period (15 and 16 patients in the CT-P42 and EU-approved Eylea groups, respectively).

Table 6: Test and reference products, doses, modes of administration and batch numbers.

Test Product, Dose and Mode of Administration, Batch Number
Test Product: CT-P42 (proposed aflibercept biosimilar) Solution for IVT injection **Presentation:** One vial/PFS of 0.05 mL contains 2 mg aflibercept **Batch Numbers:** Vial: prefilled syringe: **Mode of Administration:** IVT injection **Dose:** 2 mg/0.05 mL every 4 weeks for 5 doses, then every 8 weeks for 4 doses
Reference Product, Dose and Mode of Administration, Batch Number
Reference Product: Eylea (EU approved) Solution for IVT injection **Presentation:** One vial of 0.05 mL contains 2 mg aflibercept **Batch Numbers:** Vial: **Mode of Administration:** IVT injection **Dose:** 2 mg/0.05 mL every 4 weeks for 5 doses, then every 8 weeks for 4 doses

Concomitant Therapy

Any concomitant medication deemed necessary for the welfare of the patient during the study may have been given at the discretion of the investigator. However, it was the responsibility of the investigator to ensure that details regarding the medication were recorded in full in the source documents and eCRF. Any changes in concomitant medications were also recorded in the patient's eCRF and source documents. All concomitant medications used during the study were recorded until the last end-of-study (EOS) visit. The nondrug therapies (e.g., laser, surgery) were also collected in both the source documents and eCRF.

Treatments that were related to the IVT injection procedure or planned assessments were used in accordance with the local health authorities' guidelines for each site and were recorded in both the source documents and eCRF (e.g., drugs or agents for anaesthesia, asepsis, mydriatics, fluorescein, or topical broad-spectrum microbicide).

Fellow Eye Treatment

If the fellow (non-study) eye required any treatment, the most applicable treatment option that was approved by the governing health authorities was selected at the investigator's discretion. The fellow eye was not considered an additional study eye even though treated with aflibercept.

Only IVT aflibercept was permitted when anti-VEGF agents were considered for the fellow eye treatment during the whole study period. For the first 18 weeks of the Main Study Period, the IVT injection of aflibercept in the fellow eye was administered at least 2 weeks after and before the scheduled study drug administration. Afterwards, the IVT injections of aflibercept in the fellow eye were administered anytime including the same day as the study eye, if deemed necessary.

Prohibited Therapy

Study eye: Patients did not receive any standard or investigational agents for DME treatment in the study eye other than their assigned study drug. This included medications administered locally (e.g., IVT, by juxtascleral or periorbital routes), laser photocoagulation (panretinal or macular), and any intraocular surgeries.

Fellow eye: Anti-VEGF agents, except aflibercept, were not allowed.

Systemic: Systemic therapies, including anti-angiogenic agents and anti-angiopoietin-2 agents for DME treatment of either eye, were not permitted. Any medications that could be associated with macular oedema in the opinion of the investigator were prohibited. Also, systemic medications which included any medications that could cause vision loss or were known to be toxic to the lens, retina, or optic nerve, including (but not limited to) deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazine, and ethambutol were prohibited. Any other investigational device, medical product, or interventions of any type suspected to influence outcome (i.e., could influence the course of the underlying ocular disease or the study drug results) were not allowed.

- **Objectives**

The primary objective of this study was to demonstrate the equivalence in efficacy of CT-P42 compared to Eylea in subjects with diabetic macular oedema (DME).

Equivalence between the main treatment groups was to be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters].

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

- **Outcomes/endpoints**

The primary efficacy endpoint is the mean change from baseline in BCVA using the ETDRS chart at Week 8.

The following secondary efficacy endpoints were assessed at each applicable visit up to Week 52, and at Extension Weeks 0 and 4:

- Mean change in BCVA using the ETDRS chart from baseline
- Proportion of patients who gained ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA using the ETDRS chart
- Proportion of patients who lost ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA using the ETDRS chart
- Mean change in central subfield thickness (CST) from baseline as determined by spectral-domain optical coherence tomography
- Percentage of patients with a ≥2-step improvement from baseline in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score as assessed by fundus photography

PK Endpoints:

The following secondary PK endpoints were assessed:

- C_{max1}: maximum plasma concentration after the first study drug administration
- C_{max2}: maximum plasma concentration after the fifth study drug administration
- T_{max1}: time of observed maximum plasma concentration after the first study drug administration
- T_{max2}: time of observed maximum plasma concentration after the fifth study drug administration

Usability Endpoints:

The following secondary usability endpoints were assessed:

- Number of injections with vial kit successfully administered by healthcare professionals at Week 0
- Number of injections with PFS successfully administered by healthcare professionals at Extension Week 0

Safety Endpoints:

The following secondary safety endpoints were assessed:

- Incidence and intensity of adverse events (AEs) (ocular and non-ocular) including serious adverse events (SAEs)
- Incidence and intensity of adverse events of special interest

a) Arterial thromboembolic events (ATEs)

b) All AEs related to IVT injection procedure, including but not limited to the following: endophthalmitis, increases in intraocular pressure (IOP), intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract.

- Intraocular pressure (IOP) test, slit lamp examination, indirect ophthalmoscopy, finger count/hand motion/light perception, hypersensitivity monitoring, vital signs and weight measurement, electrocardiogram (ECG), New York Heart Association (NYHA) Functional Classification assessment, physical examination findings, pregnancy testing, and clinical laboratory analyses including haemoglobin A1c (HbA1c)
- Immunogenicity, as assessed by incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb)
- Prior and concomitant treatments.

- **Sample size**

Assuming an equivalence margin of ±3 letters with two one-sided significance levels of 0.025, a sample size of 270 patients (135 patients in each treatment group) provides an 82% statistical power to demonstrate the therapeutic equivalence of CT-P42 to Eylea based on the mean change from baseline in BCVA at Week 8. In the sample size calculation, the common SD of the mean change from baseline in BCVA was assumed as 7.438 and the expected mean difference was assumed to be 0. The dropout rate was hypothesized at 10%; therefore,

approximately 300 patients (150 patients in each treatment group of CT-P42 and Eylea) were required to be enrolled in this study.

The sample size calculation was updated in the third global version of the protocol (14.1.2022) after the first subject had been assigned to treatment (22.7.2021). In the later version a SD of 8.2 and a drop-out-rate of 12% were assumed, which resulted in a required total sample size of 360 patients is required (180 in each group) to achieve 316 patients (158 patients in each treatment group) evaluable patients.

- **Randomisation and Blinding (masking)**

Randomisation

An interactive web response system (IWRS) was used for the randomization in the Main Study Period. The study statistician had to generate the randomization schedule for the IWRS, which would link sequential patient randomization numbers to treatment codes. Patients who qualified for randomization were randomly assigned at Day 1 (Week 0) in a 1:1 ratio to the CT-P42 or Eylea treatment group.

The randomization was stratified by BCVA score (< 55 letters versus ≥ 55 letters) using the ETDRS chart on Day 1, country, and PK subgroup (Yes versus No).

Baseline BCVA was considered as a stratification factor since it is considered one of important prognostic factors (Nguyen et al. 2012; Brown et al. 2015). Country was used as one of stratification factors because it is expected to be confounded with other known or unknown prognostic factors. Following that PK evaluation was planned to be conducted in a subgroup of patients, it was considered as a stratification factor to resolve imbalance between subgroups.

The Randomization List provided specifies that block sizes of 2 and 4 were used.

Masking

The study was conducted in a double-masked manner during the Main Study Period and in an open-label manner during the Extension Study Period. The randomization codes for the Main Study Period were not to be revealed to study patients, investigators, and study centre personnel until the final CSR had been generated except for predefined unmasked personnel from Sponsor and CRO.

Under normal circumstances, the masking was not to be broken. The masking was allowed to be broken only if specific emergency treatment and medical management required the study drug to be known. In such emergencies, the investigator could determine the identity of the study drug by using the applicable procedure in the IWRS (instructions in the study manual, provided as a separate document).

The overall randomization code was to be broken only for reporting purposes. This was planned to occur after database lock for data up to Week 24 for each patient. Efficacy, PK, usability, and safety endpoints including immunogenicity were to be evaluated by the predefined unmasked personnel from Sponsor and CRO. The unmasked personnel were to be predefined and documented before performing the analyses.

- **Statistical methods**

Analysis sets for the Main Study Period

Intent-to-Treat (ITT) set was defined as all patients randomly assigned to receive either of the study drugs, regardless of whether or not any study drug was administered.

Full analysis set (FAS) was defined as all randomly assigned patients who received at least one full dose of study drug.

Per-Protocol (PP) set was defined as all randomly assigned patients who received all full doses of study drug up to Week 4 (total 2 injections) and had a BCVA assessment at Week 8. A major protocol deviation that might have affected the interpretation of study results of primary efficacy endpoint led to exclusion from PP set. Final determinations of the PP set were to be made at the masked data review meeting before unmasking.

Safety set for Main Study Period was defined as all randomized patients who receive at least one full or partial dose of study drug.

The **PK set** was defined as patients who received at least one full dose of study drug and had at least one post-treatment PK concentration data. A major protocol deviation that may affect the interpretation of study results of PK endpoints led to exclusion from PK set. Final determinations of the PK set were to be made at the masked data review meeting for the PK endpoints before unmasking.

The **Usability set** for vial kit was defined as all patients in the Safety set for Main Study Period who had evaluable usability measurements.

For the ITT, the FAS and the PP, patients were classified according to the randomized treatment group. For the Safety set for the Main Study Period and the PK set patients were classified according to the actual received treatment during the main study period, with patients receiving at least one dose of CT-P42 during the main study period allocated to the 'CT-P42' treatment group.

Analysis sets for the Extension Study Period

Safety set for Extension Study Period was defined as all patients who received full or partial dose of study drug in the Extension Study Period.

Usability set for PFS was defined as all patients in the Safety set for Extension Study Period who had evaluable usability measurements.

Primary efficacy analysis

Mean change from baseline in BCVA using the ETDRS chart at Week 8 is the primary efficacy endpoint in this study. The primary efficacy analysis was to be performed using an Analysis of Covariance (ANCOVA) model with the baseline BCVA and country as covariates and treatment group as a factor only for study eye. If country was found to be unsuitable as a covariate due to the number of levels, then this could be pooled into a new variable, region (defined as either Europe or Non-Europe), for use in the statistical model. Therapeutic equivalence of CT-P42 with respect to Eylea was to be concluded if the 2-sided 95% CI of difference of least square means (LS means) fell entirely within an equivalence margin [±3 letters]. The primary analysis set for the primary endpoint was the FAS.

Primary endpoint was also planned to be analysed using the PP set as a supportive analysis set.

Sensitivity analysis for primary efficacy endpoint

In order to evaluate the impact of missing data on the primary efficacy endpoint results, additional analyses with missing data imputation were to be conducted. Multiple imputation (MI) with the Missing at Random (MAR) assumption was to be applied using MI procedure in SAS®. All patients with non-missing baseline BCVA score in FAS were to be included in the analysis. The multiple imputed datasets were to be generated based on linear regression models on baseline BCVA score, country and treatment group as covariates. If any of covariates were missing, it was not to be considered in MI. A set of 10 imputed datasets was planned to be generated. These multiple imputed datasets were then to be analysed using the identical analysis method specified in Section 10.1.1. The results from each set of imputed data sets were then to be pooled using MIANALYZE procedure in SAS®.

Secondary analyses

Secondary endpoints were analysed descriptively and graphically.

Planned subgroup analyses

Descriptive statistics for actual result and change from baseline of BCVA at Week 8 were to be generated by treatment group and the following subgroups:

- Anti-drug antibody (ADA) positive subgroup or ADA negative subgroup
- Age (<65 or ≥65)
- Sex (male or female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Allowed by Investigator Country Regulations or Other)
- Baseline HbA1c (≤8% or >8%)
- Baseline BCVA (<40 letters, ≥40 to <55 letters, ≥55 to <65 letters, ≥65 letters)

Patients who showed at least one "Positive" result in immunogenicity test obtained after study drug exposure up to Week 8 were to be considered as "ADA positive subgroup" regardless of ADA status at pre-dose assessment. All patients who had only "Negative" results obtained after study drug exposure up to Week 8 were to be considered as "ADA negative subgroup".

Error probabilities, adjustment for multiplicity and interim analyses

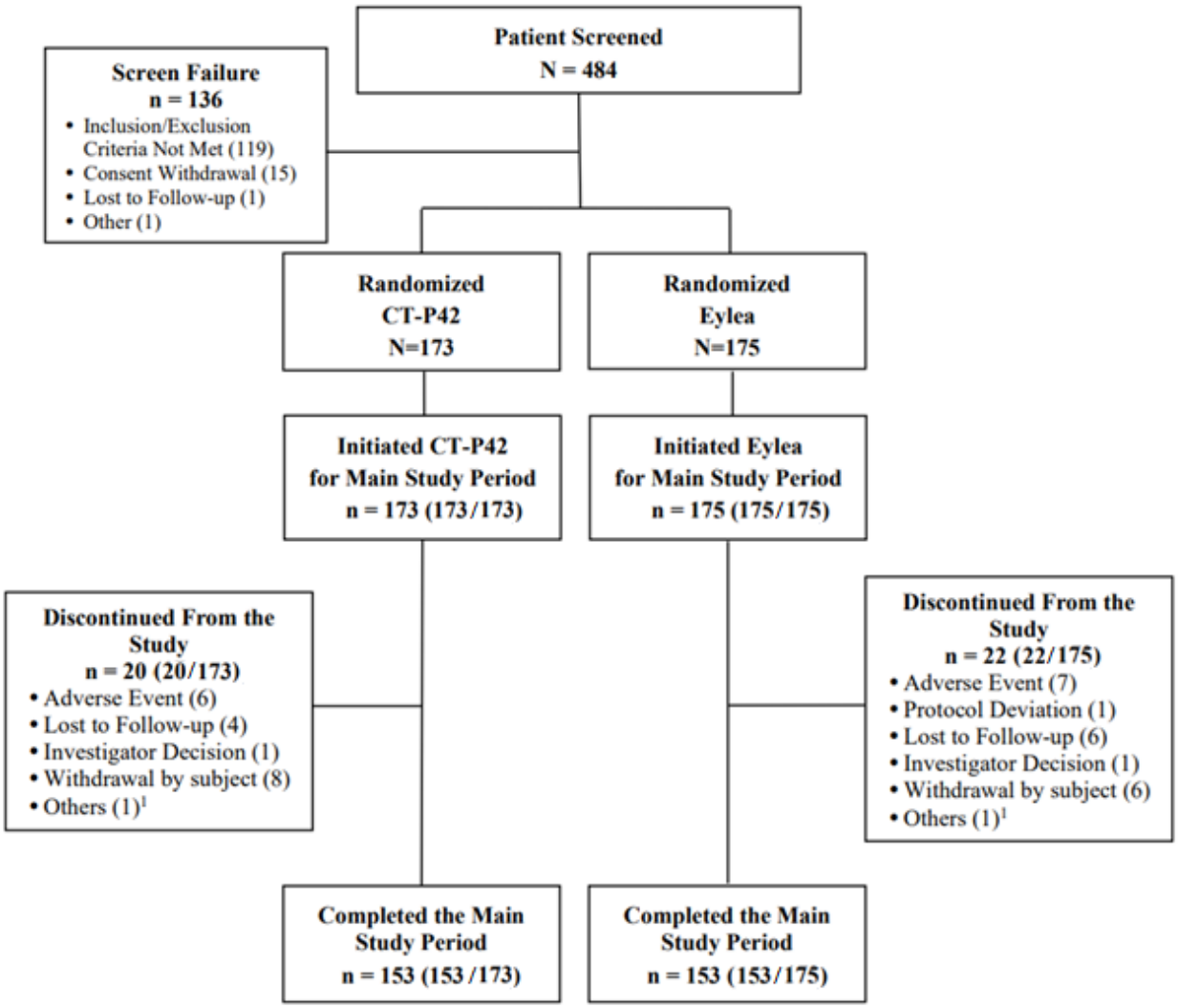
No multiple comparison adjustments for type I error were used.

Changes from protocol-specified analyses

There are two versions of the statistical analysis plan. The second version (20.7.2023) was finalized after the data base lock (19.1.2023).

Results

Figure 5: Participant flow



Two patients (1 in the CT-P42 group and 1 in the Eylea group) were discontinued from the study since they were unable to come to visit due to War in Ukraine.

- **Recruitment**

First Subject Signed Informed Consent: Jun 22, 2021

Last Subject's Visit: Apr 24, 2023

- **Conduct of the study**

After random assignment of the first patient to treatment on July 22, 2021, the global protocol was amended 2 times:

Jan 14, 2022, Amendment to Global Clinical Study Protocol - Global Version 3.0

- Removed of the condition of the axial length from exclusion criterion #2.

- Added "including potential biosimilars" to previous systemic or ocular treatment with aflibercept in exclusion criterion #5.
- Removed the time points of 12 ± 0.5 hours and 168 ± 24 hours for PK analysis.
- Updated the total number of patients and statistical assumptions for the sample size to reflect changes in the study plan.
- Added further details of sensitivity analysis and handling of missing data.
- Added details of EOS visit for patients who discontinue the study prior to the completion of Week 8 visit to reduce missing data for primary endpoint at Week 8.
- Added text to allow FA images obtained within 4 weeks prior to the first study drug administration as Screening data.
- Added detailed operation plan for DSMB.
- Updated the visit window of Week 1 visit from ±1 day to "−1 to +2 days" in the schedule of assessments.

Apr 12, 2022, Amendment to Global Clinical Study Protocol - Global Version 4.0

- Treatment period and EOS visit were retitled.
- Study design for the Extension Study Period was added.
- Changes for the Main Study Period and Extension Period were made throughout the protocol to reflect the changes in the study design.
- Time points for assessments in Extension Week 0 and 4 were added to the secondary efficacy endpoints.
- Analysis sets were retitled, and new analysis sets were added for Extension Study Period.
- Added details of usability assessment during Extension Study Period

The original protocol was amended 10 times for country specific protocols; 4 times for the United States, once for Czechia and Slovakia, and 5 times for Korea. Country specific amendments were not relevant for MA.

- **Baseline data**

Main Study period

Table 7: Demographic characteristics and stratification factors for main study period in study CT-P42 3.1 (ITT set)

	CT-P42 (N=173)	EU-Eylea (N=175)	Total (N=348)
Demographic Characteristics			
Age (years)			
n	173	175	348
Mean ± SD	62.5 ± 9.6	62.9 ± 10.3	62.7 ± 10.0
Median	63.0	63.0	63.0
Minimum, maximum	32, 85	25, 86	25, 86
Sex, n (%)			
Male	106 (61.3%)	97 (55.4%)	203 (58.3%)
Female	67 (38.7%)	78 (44.6%)	145 (41.7%)
Female Fertility Status[1], n (%)			

	CT-P42 (N=173)	EU-Eylea (N=175)	Total (N=348)
Pre-menarche	0	0	0
Surgically sterilized	5 (7.5%)	8 (10.3%)	13 (9.0%)
Post-menopausal	59 (88.1%)	67 (85.9%)	126 (86.9%)
Potentially able to bear children	3 (4.5%)	3 (3.8%)	6 (4.1%)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	61 (35.3%)	63 (36.0%)	124 (35.6%)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	112 (64.7%)	112 (64.0%)	224 (64.4%)
Not allowed by Investigator Country Regulations	0	0	0
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	5 (2.9%)	5 (2.9%)	10 (2.9%)
Non-Hispanic or non-Latino	166 (96.0%)	165 (94.3%)	331 (95.1%)
Unknown	2 (1.2%)	5 (2.9%)	7 (2.0%)
Smoking History, n (%)			
Never	121 (69.9%)	124 (70.9%)	245 (70.4%)
Current smoker	19 (11.0%)	18 (10.3%)	37 (10.6%)
Former smoker	33 (19.1%)	33 (18.9%)	66 (19.0%)
Screening Height (cm)			
n	173	175	348
Mean ± SD	165.93 ± 9.68	166.56 ± 9.19	166.25 ± 9.43
Median	164.00	167.00	166.50
Minimum, maximum	145.0, 197.0	145.0, 190.0	145.0, 197.0
Screening Weight (kg)			
n	173	175	348
Mean ± SD	78.25 ± 19.30	76.85 ± 15.78	77.55 ± 17.61
Median	75.00	75.00	75.00
Minimum, maximum	39.3, 147.0	44.0, 126.0	39.3. 147.0
Baseline HbA1c, n (%)			
≤8%	113 (65.3%)	116 (66.3%)	229 (65.8%)
>8%	60 (34.7%)	57 (32.6%)	117 (33.6%)
Stratification Factors			
Country, n (%)			
Czech Republic	19 (11.0%)	18 (10.3%)	37 (10.6%)
Estonia	1 (0.6%)	1 (0.6%)	2 (0.6%)
Hungary	21 (12.1%)	20 (11.4%)	41 (11.8%)

	CT-P42 (N=173)	EU-Eylea (N=175)	Total (N=348)
India	51 (29.5%)	53 (30.3%)	104 (29.9%)
Latvia	9 (5.2%)	5 (2.9%)	14 (4.0%)
Lithuania	0	1 (0.6%)	1 (0.3%)
Poland	19 (11.0%)	21 (12.0%)	40 (11.5%)
Republic of Korea	10 (5.8%)	10 (5.7%)	20 (5.7%)
Russian Federation	6 (3.5%)	8 (4.6%)	14 (4.0%)
Slovakia	24 (13.9%)	23 (13.1%)	47 (13.5%)
Spain	8 (4.6%)	9 (5.1%)	17 (4.9%)
Ukraine	5 (2.9%)	6 (3.4%)	11 (3.2%)
BCVA Score using ETDRS Chart on Day 1, n (%)			
< 55 letters	49 (28.3%)	46 (26.3%)	95 (27.3%)
≥ 55 letters	124 (71.7%)	129 (73.7%)	253 (72.7%)
PK Subgroup, n (%)			
Yes	12 (6.9%)	12 (6.9%)	24 (6.9%)
No	161 (93.1%)	163 (93.1%)	324 (93.1%)

[1] Percentages were calculated by using the number of female patients as the denominator

Table 8: Baseline disease characteristics of the study eye for main study period in study CT-P42 3.1 (ITT set)

	CT-P42 (N=173)	EU-Eylea (N=175)	Total (N=348)
BCVA Score at Baseline[1]			
n	173	175	348
Mean ± SD	60.3 ± 9.7	60.4 ± 10.1	60.4 ± 9.9
Median	62.0	62.0	62.0
Minimum, maximum	34, 73	34, 73	34, 73
ETDRS DRSS Score at Baseline, n (%)[1, 2]			
10	1 (0.6%)	2 (1.1%)	3 (0.9%)
20	3 (1.7%)	1 (0.6%)	4 (1.1%)
35	58 (33.5%)	60 (34.3%)	118 (33.9%)
43	48 (27.7%)	48 (27.4%)	96 (27.6%)
47	25 (14.5%)	21 (12.0%)	46 (13.2%)
53	16 (9.2%)	18 (10.3%)	34 (9.8%)
61	7 (4.0%)	5 (2.9%)	12 (3.4%)
65	3 (1.7%)	4 (2.3%)	7 (2.0%)
71	1 (0.6%)	5 (2.9%)	6 (1.7%)

	CT-P42 (N=173)	EU-Eylea (N=175)	Total (N=348)
75	0	0	0
81	0	0	0
85	0	0	0
90	11 (6.4%)	11 (6.3%)	22 (6.3%)
CST at Baseline (µm)[1,3]			
n	172	174	346
Mean ± SD	499.3 ± 138.0	483.7 ± 111.5	491.5 ± 125.4
Median	465.5	462.5	463.5
Minimum, maximum	269, 1030	274, 842	269, 1030
IOP at Baseline (mmHg)[1]			
n	174	174	348
Mean ± SD	16.0 ± 2.8	15.8 ± 2.7	15.9 ± 2.8
Median	16.0	16.0	16.0
Minimum, maximum	7, 22	9, 24	7, 24

[1] The summaries of BCVA score, DRSS score and CST at baseline were based on the FAS and the summary of IOP at baseline was based on the Safety Set for Main Study Period.
[2] DRSS score was summarized based on the severity score and presented with corresponding ETDRS severity level for clinical interpretation.

Abbreviation: IOP, intraocular pressure

Table 9: Diabetic macular oedema and diabetes mellitus history for main study period in study CT-P42 3.1 (ITT set)

	CT-P42 (N=173)	EU-Eylea (N=175)	Total (N=348)
Total Number of DM History, n	173	175	348
Number of Patients with at least 1 DM History, n (%)	173 (100.0%)	175 (100.0%)	348 (100.0%)
Duration of DM (years)[1]			
n	173	175	348

	CT-P42 (N=173)	EU-Eylea (N=175)	Total (N=348)
Mean ± SD	13.5990 ± 8.8011	14.0202 ± 9.5446	13.8108 ± 9.1717
Median	13.2074	12.3450	13.0883
Minimum, maximum	0.085, 38.973	0.104, 40.920	0.085, 40.920
Type of DM, n (%)			
Type I	14 (8.1%)	10 (5.7%)	24 (6.9%)
Type II	159 (91.9%)	165 (94.3%)	324 (93.1%)
Total Number of DME History, n	296	315	611
Number of Patients with at least 1 DME History, n (%)	173 (100.0%)	175 (100.0%)	348 (100.0%)
Location of DME, n (%)			
Unilateral	50 (28.9%)	35 (20.0%)	85 (24.4%)
OD	23 (13.3%)	21 (12.0%)	44 (12.6%)
OS	27 (15.6%)	14 (8.0%)	41 (11.8%)
Bilateral	123 (71.1%)	140 (80.0%)	263 (75.6%)
For the Study Eye			
Number of Patients with at least 1 Prior Medication for DME, n (%)[2]			
Intravitreal anti-VEGF	0	1 (0.6%)	1 (0.3%)
Intravitreal steroid	0	1 (0.6%)	1 (0.3%)
Other medication	1 (0.6%)	1 (0.6%)	2 (0.6%)
Number of Patients with at least 1 Prior Non-drug Therapy for DME, n (%)			
Laser photocoagulation	15 (8.7%)	15 (8.6%)	30 (8.6%)
Number of Patients with No Prior Treatment for DME, n (%)	157 (90.8%)	160 (91.4%)	317 (91.1%)
Duration of DME (years)[1]			
n	173	175	348
Mean ± SD	0.5913 ± 1.4285	0.8395 ± 1.9134	0.7161 ± 1.6919
Median	0.1451	0.1807	0.1684
Minimum, maximum	0.0, 14.185	0.0, 14.346	0.0, 14.346

[1] Durations of DM and DME were calculated as ([the first administration date of study drug – start date of disease]/365.25).
[2] A patient was counted only once for each type of prior treatment for DME. A prior medication for DME other than IVT anti-VEGF and IVT Steroid was summarized as 'Other medication'.
Abbreviations: OD, oculus dexter (right eye); OS, oculus sinister (left eye)

Extension study period

Table 10: Demographic characteristics for extension study period in study CT-P42 3.1 (safety set for extension study period)

	CT-P42 (N=31)
Demographic Characteristics	
Age (years)	
n	31
Mean ± SD	64.7 ± 10.8
Median	68.0
Minimum, maximum	32, 81
Sex, n (%)	
Male	18 (58.1%)
Female	13 (41.9%)
Female Fertility Status[1], n (%)	
Pre-menarche	0
Surgically sterilized	0
Post-menopausal	13 (100.0%)
Potentially able to bear children	0
Race, n (%)	
American Indian or Alaska Native	0
Asian	0
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	31 (100.0%)
Not allowed by Investigator Country Regulations	0
Other	0
Ethnicity, n (%)	
Hispanic or Latino	2 (6.5%)
Non-Hispanic or non-Latino	29 (93.5%)
Unknown	0
Smoking History, n (%)	
Never	17 (54.8%)
Current smoker	5 (16.1%)
Former smoker	9 (29.0%)

	CT-P42 (N=31)
Screening Height (cm)	
n	31
Mean ± SD	169.00 ± 7.96
Median	170.00
Minimum, maximum	155.0, 185.0
Screening Weight (kg)	
n	31
Mean ± SD	82.93 ± 17.83
Median	80.00
Minimum, maximum	52.0, 122.0
Baseline HbA1c, n (%)	
≤8%	16 (51.6%)
>8%	15 (48.4%)

[1] Percentages were calculated by using the number of female patients as the denominator.

Medical history

Overall, 100 (28.7%) patients (49 [28.2%] patients in the CT-P42 group and 51 [29.3%] patients in the Eylea group) had taken at least 1 prior medication. The most frequently reported prior medications by drug class were ophthalmologicals (31 [17.8%] patients in the CT-P42 group and 31 [17.8%] patients in the Eylea group), followed by vaccines (21 [12.1%] patients in the CT-P42 group and 17 [9.8%] patients in the Eylea group). Overall, 36 (10.3%) patients (18 [10.3%] patients in the CT-P42 group and 18 [10.3%] patients in the Eylea group) had taken at least 1 prior nondrug therapy for DME. All these patients had prior nondrug therapy of retinal laser coagulation. The proportion of patients with prior medications and prior nondrug therapy for DME were balanced between the treatment groups.

Concomitant treatments – Main study Period

All patients in the safety set for Main Study Period had taken at least 1 concomitant medication. The most frequently reported concomitant medication was drug used in diabetes and ophthalmologicals (174 [100.0%] patients in the CT-P42 group and 174 [100.0%] patients in the Eylea group), followed by agents acting on the renin-angiotensin system (107 [61.5%] patients in the CT-P42 group and 113 [64.9%] patients in the Eylea group). The commonly used concomitant medications were typical use in this patient population or required as part of the study procedures. The proportions of patients for each class were generally similar between the treatment groups. Overall, 3 (0.9%) patients in the safety set for Main Study Period (1 [0.6%] patient in the CT-P42 group and 2 [1.1%] patients in the Eylea group) had taken at least 1 concomitant nondrug therapy for DME. These 3 patients had nondrug therapy of retinal laser coagulation in the fellow eye.

Concomitant treatments – Extension Study Period

5 (16.1%) patients in the safety set for Extension Study Period had taken at least 1 concomitant medication during the Extension Study Period. The most frequently reported concomitant medication was ophthalmologicals (4 [12.9%] patients). No patients had taken nondrug therapy for the DME during the Extension Study Period.

- **Numbers analysed**

Numbers analysed

Table 11: Analysis set for main study period (all randomly assigned patients)

	CT-P42 (N=173)	Eylea (N=175)	Total (N=348)
Main Study Period, n			
ITT set	173	175	348
FAS	173	175	348
PP set	165	167	332
PK set	11	12	23
Safety set for Main Study Period[1]	174	174	348
Usability set for vial kit	45	50	95

Abbreviations: FAS, full analysis set; ITT, intent-to-treat; n, number of patients within a specific category; PK, pharmacokinetic; PP, per-protocol.

Outcomes and estimation

Primary efficacy analysis

The primary efficacy endpoint is the mean change from baseline in BCVA using the ETDRS chart at Week 8. The primary efficacy analysis was conducted on the FAS using an ANCOVA model and a supportive analysis for the primary efficacy endpoint was conducted using the PP Set.

Table 12: Statistical analysis of mean change from baseline in BCVA at week 8 by treatment (ANCOVA) in study CT-P42 3.1 (FAS and PP set)

Treatment Group	n	LS Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
FAS				
CT-P42	169	9.43 (0.798)	0.58	(-0.73, 1.88)
EU-approved Eylea	172	8.85 (0.775)		
PP Set				
CT-P42	165	9.22 (0.837)	0.38	(-0.90, 1.66)
EU- Eylea	167	8.84 (0.840)		

Note: An ANCOVA was performed with change from baseline in BCVA at Week 8 as the dependent variable, treatment as a factor, and baseline BCVA and country as covariates. Statistical analyses for primary efficacy endpoint were conducted only for the study eye.

Sensitivity analysis

Sensitivity analysis was performed to assess the impact of missing data using multiple imputation with the missing at random assumptions.

Table 13: Statistical analysis of mean change from baseline in BCVA at week 8 by treatment (ANCOVA) – multiple imputation in study CT-P42 3.1 (FAS)

Treatment Group	n (*)	LS Mean (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
CT-P42	173 (169)	9.44 (0.799)	0.60	(-0.70, 1.90)
EU-approved Eylea	175 (172)	8.84 (0.775)		

Note: An ANCOVA was performed with change from baseline in BCVA at Week 8 as the dependent variable, treatment as a factor, and baseline BCVA and country as covariates. All patients with non-missing baseline BCVA score in FAS were included in this analysis. Multiple imputation (MI) with the MAR assumption was used for missing data imputation. Statistical analyses for primary efficacy endpoint were conducted only for the study eye.
* The number of patients with non-missing values at baseline visit and Week 8 in the FAS is presented in the parenthesis.

Secondary efficacy endpoints

1. **Mean change in BCVA from baseline**

Main study period

Figure 6: Mean (± SD) Change from baseline in BCVA by visit for main study period in study CT-P42 3.1 (FAS)

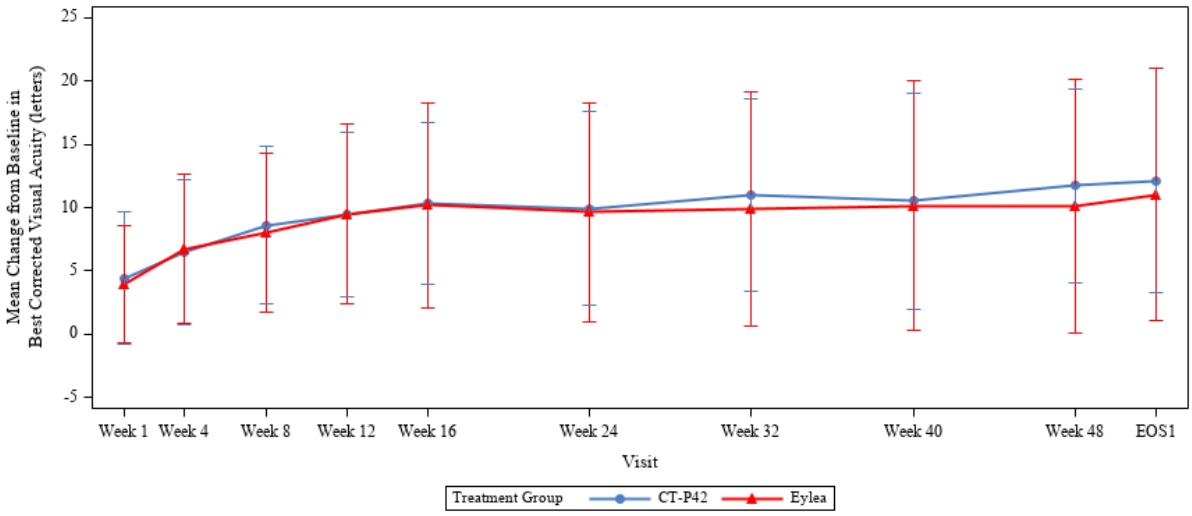


Table 14: Descriptive statistics for actual value and change from baseline of BCVA for main study period in study CT-P42 3.1 (FAS)

Visit Statistic	CT-P42 (N=173) Actual Result	CT-P42 (N=173) Change From Baseline	EU-approved Eylea (N=175) Actual Result	EU-approved Eylea (N=175) Change From Baseline
Baseline				
n	173	-	175	-
Mean ± SD	60.3 ± 9.7	-	60.4 ± 10.1	-
Median	62.0	-	62.0	-
Minimum, maximum	34, 73	-	34, 73	-
Week 1				
n	169	169	172	172
Mean ± SD	64.6 ± 11.7	4.4 ± 5.3	64.4 ± 10.5	4.0 ± 4.6
Median	68.0	3.0	66.0	3.5
Minimum, maximum	34, 94	-16, 27	35, 88	-5, 21
Week 4				
n	172	172	173	173
Mean ± SD	66.8 ± 11.7	6.5 ± 5.7	67.3 ± 10.7	6.7 ± 5.9
Median	69.5	6.5	69.0	5.0
Minimum, maximum	33, 93	-7, 21	37, 88	-8, 25
Week 8				
n	169	169	172	172
Mean ± SD	69.1 ± 11.8	8.6 ± 6.2	68.5 ± 11.1	8.0 ± 6.3
Median	72.0	8.0	70.5	7.0
Minimum, maximum	32, 92	-7, 27	34, 93	-18, 25
Week 12				
n	168	168	165	165
Mean ± SD	69.9 ± 11.9	9.5 ± 6.5	70.0 ± 10.9	9.5 ± 7.1
Median	73.0	10.0	72.0	9.0
Minimum, maximum	33, 94	-10, 25	35, 92	-17, 43
Week 16				
n	166	166	165	165
Mean ± SD	70.8 ± 11.6	10.3 ± 6.4	70.8 ± 11.4	10.2 ± 8.1
Median	73.0	11.0	73.0	10.0
Minimum, maximum	25, 93	-14, 26	30, 94	-22, 47
Week 24				
n	165	165	164	164
Mean ± SD	70.5 ± 12.4	9.9 ± 7.6	70.3 ± 11.9	9.7 ± 8.6
Median	73.0	10.0	73.0	10.0

Visit Statistic	CT-P42 (N=173) Actual Result	 Change From Baseline	EU-approved Eylea (N=175) Actual Result	 Change From Baseline
Minimum, maximum	25, 94	-31, 27	30, 91	-43, 31
Week 32				
n	160	160	159	159
Mean ± SD	72.1 ± 11.4	11.0 ± 7.6	70.5 ± 12.5	9.9 ± 9.2
Median	74.0	10.0	73.0	11.0
Minimum, maximum	27, 96	-12, 33	22, 90	-51, 31
Week 40				
n	155	155	154	154
Mean ± SD	71.7 ± 12.3	10.5 ± 8.6	70.9 ± 12.6	10.2 ± 9.8
Median	74.0	11.0	74.0	10.0
Minimum, maximum	33, 99	-30, 33	23, 91	-50, 31
Week 48				
n	153	153	153	153
Mean ± SD	73.0 ± 11.3	11.7 ± 7.7	70.8 ± 13.0	10.1 ± 10.1
Median	75.0	12.0	74.0	11.0
Minimum, maximum	22, 93	-32, 31	24, 92	-46, 35
Week 52/EOS1				
n	156	156	156	156
Mean ± SD	73.1 ± 11.9	12.1 ± 8.9	71.5 ± 12.7	11.1 ± 9.9
Median	75.0	12.0	74.0	11.5
Minimum, maximum	21, 94	-38, 33	25, 95	-46, 35

Extension study period

Table 15 : Descriptive statistics for actual value and change from baseline of BCVA for extension study period in study CT-P42 3.1 (safety set for extension study period)

Visit Statistic	CT-P42 (N=31) Actual Result	 Change From Baseline
Baseline[1]		
n	31	-
Mean ± SD	60.9 ± 9.4	-
Median	63.0	-
Minimum, maximum	35, 73	-

Visit Statistic	CT-P42 (N=31) Actual Result	 Change From Baseline
Extension Week 0		
n	31	31
Mean ± SD	72.4 ± 10.2	11.5 ± 6.8
Median	74.0	12.0
Minimum, maximum	51, 88	-1, 27
Extension Week 4/EOS2		
n	31	31
Mean ± SD	72.3 ± 10.2	11.3 ± 7.1
Median	72.0	11.0
Minimum, maximum	49, 85	-2, 27

[1] Actual results of BCVA at baseline of Main Study Period are included

2. Proportion of Patients Who Gained or Lost ≥ 5, ≥ 10, and ≥ 15 ETDRS letters From Baseline in BCVA

Main Study Period

Table 16: Proportion of patients who gained or lost ⩾ 5, ⩾ 10, and ⩾ 15 ETDRS letters from baseline in BCVA for main study period in study CT-P42 3.1 (FAS)

Visit Category Range	CT-P42 (N=173)	EU-approved Eylea (N=175)	Total (N=348)
Week 1, n (%)			
Gained			
≥ 5 letters	73 (42.2%)	71 (40.6%)	144 (41.4%)
≥ 10 letters	26 (15.0%)	23 (13.1%)	49 (14.1%)
≥ 15 letters	10 (5.8%)	5 (2.9%)	15 (4.3%)
Lost			
≥ 5 letters	3 (1.7%)	2 (1.1%)	5 (1.4%)
≥ 10 letters	1 (0.6%)	0	1 (0.3%)
≥ 15 letters	1 (0.6%)	0	1 (0.3%)
Week 4, n (%)			
Gained			

Visit Category Range	CT-P42 (N=173)	EU-approved Eylea (N=175)	Total (N=348)
≥ 5 letters	110 (63.6%)	108 (61.7%)	218 (62.6%)
≥ 10 letters	53 (30.6%)	47 (26.9%)	100 (28.7%)
≥ 15 letters	17 (9.8%)	23 (13.1%)	40 (11.5%)
Lost			
≥ 5 letters	5 (2.9%)	1 (0.6%)	6 (1.7%)
≥ 10 letters	0	0	0
≥ 15 letters	0	0	0
Week 8, n (%)			
Gained			
≥ 5 letters	133 (76.9%)	119 (68.0%)	252 (72.4%)
≥ 10 letters	65 (37.6%)	66 (37.7%)	131 (37.6%)
≥ 15 letters	26 (15.0%)	26 (14.9%)	52 (14.9%)
Lost			
≥ 5 letters	4 (2.3%)	3 (1.7%)	7 (2.0%)
≥ 10 letters	0	2 (1.1%)	2 (0.6%)
≥ 15 letters	0	1 (0.6%)	1 (0.3%)
Week 12, n (%)			
Gained			
≥ 5 letters	136 (78.6%)	129 (73.7%)	265 (76.1%)
≥ 10 letters	91 (52.6%)	71 (40.6%)	162 (46.6%)
≥ 15 letters	32 (18.5%)	29 (16.6%)	61 (17.5%)
Lost			
≥ 5 letters	3 (1.7%)	1 (0.6%)	4 (1.1%)
≥ 10 letters	1 (0.6%)	1 (0.6%)	2 (0.6%)
≥ 15 letters	0	1 (0.6%)	1 (0.3%)
Week 16, n (%)			
Gained			
≥ 5 letters	140 (80.9%)	133 (76.0%)	273 (78.4%)
≥ 10 letters	93 (53.8%)	92 (52.6%)	185 (53.2%)

Visit Category Range	CT-P42 (N=173)	EU-approved Eylea (N=175)	Total (N=348)
≥ 15 letters	36 (20.8%)	39 (22.3%)	75 (21.6%)
Lost			
≥ 5 letters	1 (0.6%)	3 (1.7%)	4 (1.1%)
≥ 10 letters	1 (0.6%)	3 (1.7%)	4 (1.1%)
≥ 15 letters	0	2 (1.1%)	2 (0.6%)
Week 24, n (%)			
Gained			
≥ 5 letters	139 (80.3%)	131 (74.9%)	270 (77.6%)
≥ 10 letters	94 (54.3%)	90 (51.4%)	184 (52.9%)
≥ 15 letters	44 (25.4%)	42 (24.0%)	86 (24.7%)
Lost			
≥ 5 letters	5 (2.9%)	7 (4.0%)	12 (3.4%)
≥ 10 letters	2 (1.2%)	4 (2.3%)	6 (1.7%)
≥ 15 letters	1 (0.6%)	2 (1.1%)	3 (0.9%)
Week 32, n (%)			
Gained			
≥ 5 letters	135 (78.0%)	125 (71.4%)	260 (74.7%)
≥ 10 letters	95 (54.9%)	95 (54.3%)	190 (54.6%)
≥ 15 letters	46 (26.6%)	39 (22.3%)	85 (24.4%)
Lost			
≥ 5 letters	3 (1.7%)	9 (5.1%)	12 (3.4%)
≥ 10 letters	2 (1.2%)	4 (2.3%)	6 (1.7%)
≥ 15 letters	0	2 (1.1%)	2 (0.6%)
Week 40, n (%)			
Gained			
≥ 5 letters	128 (74.0%)	121 (69.1%)	249 (71.6%)
≥ 10 letters	95 (54.9%)	89 (50.9%)	184 (52.9%)
≥ 15 letters	45 (26.0%)	43 (24.6%)	88 (25.3%)
Lost			
≥ 5 letters	7 (4.0%)	8 (4.6%)	15 (4.3%)

Visit Category Range	CT-P42 (N=173)	EU-approved Eylea (N=175)	Total (N=348)
≥ 10 letters	3 (1.7%)	6 (3.4%)	9 (2.6%)
≥ 15 letters	3 (1.7%)	1 (0.6%)	4 (1.1%)
Week 48, n (%)			
Gained			
≥ 5 letters	133 (76.9%)	121 (69.1%)	254 (73.0%)
≥ 10 letters	103 (59.5%)	88 (50.3%)	191 (54.9%)
≥ 15 letters	51 (29.5%)	47 (26.9%)	98 (28.2%)
Lost			
≥ 5 letters	3 (1.7%)	11 (6.3%)	14 (4.0%)
≥ 10 letters	1 (0.6%)	6 (3.4%)	7 (2.0%)
≥ 15 letters	1 (0.6%)	4 (2.3%)	5 (1.4%)
Week 52/EOS1, n (%)			
Gained			
≥ 5 letters	138 (79.8%)	127 (72.6%)	265 (76.1%)
≥ 10 letters	105 (60.7%)	98 (56.0%)	203 (58.3%)
≥ 15 letters	60 (34.7%)	52 (29.7%)	112 (32.2%)
Lost			
≥ 5 letters	4 (2.3%)	9 (5.1%)	13 (3.7%)
≥ 10 letters	2 (1.2%)	6 (3.4%)	8 (2.3%)
≥ 15 letters	2 (1.2%)	3 (1.7%)	5 (1.4%)

Extension study period

Table 17 : Proportion of patients who gained or lost ⩾ 5, ⩾ 10, and ⩾ 15 ETDRS letters from baseline in BCVA for extension study period in study CT-P42 3.1 (safety set for extension study period)

Visit Category Range	CT-P42 (N=31)
Extension Week 0, n (%)	
Gained	
≥ 5 letters	26 (83.9%)

Visit Category Range	CT-P42 (N=31)
≥ 10 letters	19 (61.3%)
≥ 15 letters	12 (38.7%)
Lost	
≥ 5 letters	0
≥ 10 letters	0
≥ 15 letters	0
Extension Week 4/EOS2, n (%)	
Gained	
≥ 5 letters	25 (80.6%)
≥ 10 letters	17 (54.8%)
≥ 15 letters	10 (32.3%)
Lost	
≥ 5 letters	0
≥ 10 letters	0
≥ 15 letters	0

3. Mean change in CST from baseline

Main study period

Figure 7: Mean (± SD) Change from Baseline in CST (µm) by Visit in Study CT-P42 3.1 (FAS)

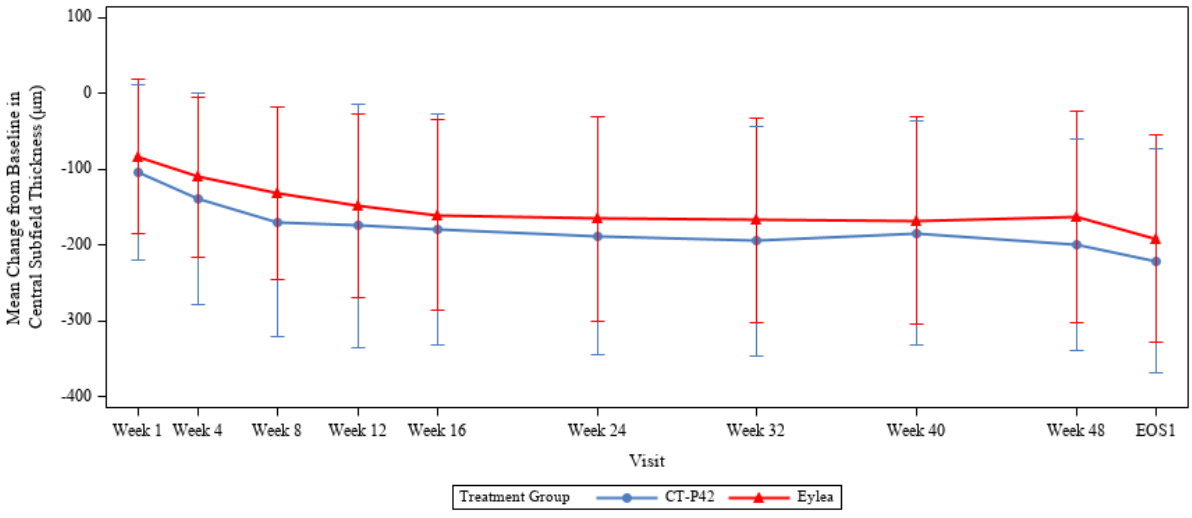


Table 18: Descriptive statistics for actual value and change from baseline of CST (µm) in study CT-P42 3.1 (FAS)

Visit Statistic	CT-P42 (N=173) Actual Result	CT-P42 (N=173) Change From Baseline	EU-approved Eylea (N=175) Actual Result	EU-approved Eylea (N=175) Change From Baseline
Baseline				
n	172	-	174	-
Mean ± SD	499.3 ± 138.0	-	483.7 ± 111.5	-
Median	465.5	-	462.5	-
Minimum, maximum	269, 1030	-	274, 842	-
Week 1				
n	165	165	169	169
Mean ± SD	392.5 ± 94.4	-104.0 ± 115.0	401.1 ± 99.5	-83.5 ± 101.8
Median	375.0	-70.0	391.0	-48.0
Minimum, maximum	155, 733	-581, 48	207, 772	-473, 46
Week 4				
n	169	169	171	171
Mean ± SD	361.7 ± 105.6	-139.4 ± 139.8	371.8 ± 95.2	-109.8 ± 105.7
Median	346.0	-93.0	356.0	-85.0
Minimum, maximum	159, 842	-746, 122	180, 729	-479, 153
Week 8				
n	167	167	167	167
Mean ± SD	330.1 ± 89.5	-169.2 ± 152.2	350.0 ± 86.9	-131.2 ± 113.7
Median	314.0	-130.0	344.0	-102.0
Minimum, maximum	148, 661	-770, 136	163, 713	-484, 140
Week 12				
n	166	166	164	164
Mean ± SD	323.4 ± 88.4	-174.4 ± 160.7	334.1 ± 84.2	-148.5 ± 121.2
Median	301.0	-148.5	322.5	-121.0
Minimum, maximum	173, 662	-782, 288	154, 690	-488, 85
Week 16				
n	159	159	162	162
Mean ± SD	312.1 ± 83.2	-179.2 ± 153.3	321.2 ± 86.0	-160.5 ± 125.7
Median	292.0	-152.0	302.5	-120.5
Minimum, maximum	159, 587	-777, 61	191, 708	-571, 102
Week 24				
n	163	163	160	160
Mean ± SD	310.8 ± 91.8	-187.5 ± 156.8	316.0 ± 99.4	-165.1 ± 134.7
Median	289.0	-157.0	296.5	-132.0
Minimum, maximum	170, 738	-768, 155	150, 758	-671, 120

Visit Statistic	CT-P42 (N=173) Actual Result	 Change From Baseline	EU-approved Eylea (N=175) Actual Result	 Change From Baseline
Week 32				
n	158	158	157	157
Mean ± SD	300.4 ± 83.4	-194.5 ± 151.6	316.2 ± 92.7	-166.9 ± 134.6
Median	279.5	-160.0	293.0	-135.0
Minimum, maximum	167, 644	-769, 58	156, 729	-665, 105
Week 40				
n	151	151	147	147
Mean ± SD	303.3 ± 97.1	-184.0 ± 147.5	313.3 ± 103.1	-167.3 ± 136.7
Median	275.0	-166.0	287.0	-146.0
Minimum, maximum	184¸706	-764, 213	150, 786	-612, 148
Week 48				
n	149	149	149	149
Mean ± SD	288.5 ± 77.1	-199.8 ± 139.2	317.3 ± 116.6	-162.6 ± 140.3
Median	268.0	-175.0	283.0	-133.0
Minimum, maximum	181, 527	-623, 74	151, 831	-615, 172
Week 52/EOS1				
n	151	151	154	154
Mean ± SD	271.0 ± 66.6	-220.7 ± 147.1	288.9 ± 82.1	-191.2 ± 137.0
Median	257.0	-191.0	273.5	-164.5
Minimum, maximum	169, 538	-746¸ 73	146, 642	-659, 204

4. Proportion of Patients with a ≥ 2-Step Improvement From Baseline in the ETDRS DRSS Score

Table 19: Summary of patients with ≥ 2-step improvement from baseline in ETDRS DRSS score in study CT-P42 3.1 (FAS)

Visit	CT-P42 (N=173)	EU-approved Eylea (N=175)	Total (N=348)
Week 8, n (%)	27 (15.6%)	28 (16.0%)	55 (15.8%)
Week 24, n (%)	41 (23.7%)	35 (20.0%)	76 (21.8%)
Week 52/EOS1, n (%)	41 (23.7%)	38 (21.7%)	79 (22.7%)

Note: 2-step improvement is defined as a case of the patient whose post-baseline severity score decreases by 2 or more classes compared to the baseline value.

- **Ancillary analyses**

Table 20: Descriptive statistics for actual value and change from baseline of BCVA at Week 8 by subgroup in study CT-P42 3.1 (FAS)

Subgroup Statistic	CT-P42 (N=173)		EU-approved Eylea (N=175)	
	Actual Result	Change From Baseline	Actual Result	Change From Baseline
FAS				
n	169	169	172	172
Mean ± SD	69.1 ± 11.8	8.6 ± 6.2	68.5 ± 11.1	8.0 ± 6.3
Median	72.0	8.0	70.5	7.0
Minimum, maximum	32, 92	-7, 27	34, 93	-18, 25
ADA Positive Subgroup				
n	3	3	2	2
Mean ± SD	78.3 ± 13.5	10.7 ± 11.0	86.5 ± 2.1	14.5 ± 0.7
Median	78.0	10.0	86.5	14.5
Minimum, maximum	65, 92	0, 22	85, 88	14, 15
ADA Negative Subgroup				
n	164	164	164	164
Mean ± SD	68.8 ± 11.7	8.6 ± 6.2	68.3 ± 11.0	7.8 ± 6.3
Median	72.0	8.0	70.0	7.0
Minimum, maximum	32, 91	-7, 27	34, 93	-18, 25
Age < 65 years				
n	97	97	92	92
Mean ± SD	69.6 ± 11.4	9.4 ± 6.2	68.2 ± 11.9	8.5 ± 6.0
Median	72.0	9.0	70.0	8.0
Minimum, maximum	35, 92	-5, 27	37,93	-11, 24
Age ≥ 65 years				
n	72	72	80	80
Mean ± SD	68.3 ± 12.3	7.5 ± 6.1	68.9 ± 10.2	7.4 ± 6.6
Median	71.5	8.0	72.0	7.0
Minimum, maximum	32,89	-7,23	34, 86	-18, 25
Male				
n	104	104	96	96
Mean ± SD	70.5 ± 11.1	9.7 ± 6.6	69.6 ± 10.8	8.3 ± 6.8
Median	72.5	9.0	71.0	7.0
Minimum, maximum	35, 92	-6, 27	34, 93	-18, 25
Female				
n	65	65	76	76
Mean ± SD	66.7 ± 12.5	7.0 ± 5.2	67.1 ± 11.3	7.6 ± 5.5
Median	70.0	8.0	70.0	7.0
Minimum, maximum	32, 85	-7, 18	37, 85	-9, 20
Asian				
n	59	59	62	62

Subgroup Statistic	CT-P42 (N=173)		EU-approved Eylea (N=175)	
	Actual Result	Change From Baseline	Actual Result	Change From Baseline
Mean ± SD	65.4 ± 9.5	7.7 ± 5.4	64.5 ± 10.5	7.6 ± 5.6
Median	65.0	8.0	63.5	6.5
Minimum, maximum	43, 84	-6, 27	43, 88	0, 22
White				
n	110	110	110	110
Mean ± SD	71.0 ± 12.4	9.1 ± 6.5	70.8 ± 10.8	8.2 ± 6.6
Median	74.0	9.0	73.0	8.0
Minimum, maximum	32, 92	-7, 25	34, 93	-18, 25
Baseline HbA1c ≤ 8 %				
n	109	109	113	113
Mean ± SD	69.5 ± 12.0	8.9 ± 6.6	69.1 ± 11.0	8.0 ± 6.7
Median	72.0	9.0	72.0	7.0
Minimum, maximum	32, 92	-7, 27	34, 93	-18, 25
Baseline HbA1c > 8 %				
n	60	60	57	57
Mean ± SD	68.2 ± 11.4	8.2 ± 5.5	67.6 ± 11.2	8.0 ± 5.5
Median	72.0	7.5	70.0	7.0
Minimum, maximum	40, 85	-5, 24	37, 87	0, 22
Baseline BCVA < 40 letters				
n	9	9	6	6
Mean ± SD	42.6 ± 6.8	5.9 ± 6.7	47.7 ± 8.7	11.2 ± 7.3
Median	43.0	5.0	46.0	10.0
Minimum, maximum	32, 52	-4, 16	37, 60	1, 22
Baseline BCVA ≥ 40 to < 55 letters				
n	38	38	39	39
Mean ± SD	57.6 ± 8.0	7.3 ± 6.9	57.2 ± 8.7	9.3 ± 8.1
Median	57.5	7.0	55.0	9.0
Minimum, maximum	41, 80	-7, 27	34, 74	-18, 25
Baseline BCVA ≥ 55 to < 65 letters				
n	52	52	52	52
Mean ± SD	71.0 ± 6.3	10.7 ± 5.9	66.9 ± 6.2	7.4 ± 5.5
Median	71.0	10.0	66.5	7.0
Minimum, maximum	60, 85	0, 24	50, 80	-9, 19
Baseline BCVA ≥ 65 letters				
n	70	70	75	75
Mean ± SD	77.3 ± 5.8	8.2 ± 5.6	77.2 ± 5.8	7.5 ± 5.5
Median	77.0	8.0	77.0	7.0
Minimum, maximum	64, 92	-5, 25	55, 93	-11, 24

Subgroup Statistic	CT-P42 (N=173)		EU-approved Eylea (N=175)	
	Actual Result	Change From Baseline	Actual Result	Change From Baseline

Note: Patients who showed at least one "Positive" result in immunogenicity test obtained after study drug exposure up to Week 8 were considered as "ADA positive subgroup" regardless of ADA status at pre-dose assessment. All patients who had only "Negative" results obtained after study drug exposure up to Week 8 were considered as "ADA negative subgroup".

Statistical analysis of mean change from baseline in CST of study eye by treatment

By request, the applicant conducted statistical analyses of the difference between CT-P42 and Eylea in the mean change from baseline (CFB) in CST at all timepoints using both a t-test and an analysis of covariance (ANCOVA) model with 95% confidence interval (CI). In the ANCOVA model, country and baseline CST were used as covariates and treatment group as a factor for the study eye. (Table 21).

Table 21: Statistical analysis of mean CFB in CST (µm) of study eye by treatment (FAS)

Visit	Treatment	n	No adjustment[1]		Adjustment for Country and Baseline CST[2]	
			Estimate of Treatment Difference in Means (CT-P42-Eylea)	95% CI	Estimate of Treatment Difference in LS Means (CT-P42-Eylea)	95% CI
Week 1	CT-P42	165	-20.44	(-43.81,2.92)	-12.56	(-30.31,5.19)
	Eylea	169				
Week 4	CT-P42	169	-29.60	(-56.01,-3.18)	-16.07	(-35.87,3.73)
	Eylea	171				
Week 8	CT-P42	167	-38.04	(-66.96,-9.12)	-22.30	(-41.06,-3.55)
	Eylea	167				
Week 12	CT-P42	166	-25.91	(-56.76,4.94)	-11.07	(-29.80,7.66)
	Eylea	164				
Week 16	CT-P42	159	-18.78	(-49.53,11.98)	-8.84	(-27.54,9.86)
	Eylea	162				
Week 24	CT-P42	163	-22.39	(-54.41,9.63)	-5.58	(-26.72,15.55)
	Eylea	160				
Week 32	CT-P42	158	-27.63	(-59.42,4.16)	-16.50	(-36.27,3.28)
	Eylea	157				
Week 40	CT-P42	151	-16.70	(-49.15,15.75)	-10.78	(-33.55,11.99)
	Eylea	147				
Week 48	CT-P42	149	-37.17	(-69.02,-5.31)	-29.79	(-52.13,-7.45)
	Eylea	149				
Week 52	CT-P42	148	-27.93	(-60.31,4.46)	-16.55	(-33.11,0.02)
	Eylea	149				

Abbreviations: CFB, change from baseline; CI, confidence interval; CST, central subfield thickness; FAS, full-analysis set; LS, least squares; n, the number of patients with CST measured at each visit.
Note: [1]The estimated mean difference between CT-P42 and Eylea and its two-sided 95% CI were calculated using a t-test. [2]An analysis of covariance (ANCOVA) was performed with change from baseline in CST as the dependent variable, treatment as a factor, and country and baseline CST as covariates. Statistical analyses were conducted only for study eye. The result at Week 52 only took into account the results from patients who completed the main study period by Week 48.

- **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 CT-P42 3.1

Title: A Randomized, Active-Controlled, Double-Masked, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P42 in Comparison with Eylea in Patients with Diabetic Macular Edema			
Study identifier	CT-P42 3.1 (protocol number), 2020-004278-23 (EudraCT Number)		
Design	Randomized, active-controlled, double-masked, parallel, multicentre clinical Phase 3 study to evaluate the efficacy, PK, usability, and overall safety including immunogenicity of CT-P42 compared with EU Eylea via IVT injection using a single dose vial kit followed by a 4-week open-label, single-arm extension study to evaluate the usability, efficacy and safety of CT-P42 via IVT injection using a PFS in patients with DME		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable 4 weeks (only subgroup of patients)	
Hypothesis	Equivalence		
Treatments groups in the Main Study Period	CT-P42 (N=173 randomized)	Subjects randomized to CT-P42 were administered 2 mg/0.05 mL CT-P42 injection using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses, for a total of 52 weeks. In this treatment group, 15 patients entered the extension phase to obtain one additional dose of CT-P42 after the main study period.	
	EU-approved Eylea (N=175 randomized)	Subjects randomized to EU-approved Eylea were administered 2 mg/0.05 mL EU-approved Eylea IVT injection using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses, for a total of 52 weeks. In this treatment group, 16 patients entered the extension phase to obtain one dose of CT-P42 after the main study period.	
Endpoints and definitions	Primary endpoint	Change from baseline in Best Corrected Visual Acuity using the ETDRS chart at Week 8	
Database lock	19.1.2023 (for the week 24 data)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): FAS consists of all randomly assigned patients who received at least one full dose of study drug. Patients were analysed according to the treatment group they were assigned to at randomization. **Week 8**		
Descriptive statistics and estimate variability	Treatment group	CT-P42	EU-approved Eylea
	Number of subjects	169	172

Title: A Randomized, Active-Controlled, Double-Masked, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P42 in Comparison with Eylea in Patients with Diabetic Macular Edema			
Study identifier	CT-P42 3.1 (protocol number), 2020-004278-23 (EudraCT Number)		
	Method: based on available cases LS Means (Standard Error) of change from baseline in BCVA at Week 8	9.43 (0.798)	8.85 (0.775)
	LS Mean difference (CT-P42 – Eylea) [95% CI]	0.58 [-0.73, 1.88]	
Analysis description	**Sensitivity analysis of Primary Efficacy Variable**		
Analysis population and time point description	Full Analysis Set (FAS): **Week 8**		
Descriptive statistics and estimate variability	Treatment group	CT-P42	EU-approved Eylea
	Number of subjects	173	175
	Method: Multiple Imputation based on Missing-at-Random assumption LS Means (Standard Error) of change from baseline in BCVA at Week 8	9.44 (0.799)	8.84 (0.775)
	LS Mean difference (CT-P42 – Eylea) [95% CI]	0.60 [-0.70, 1.90]	
Analysis description	**Supportive analysis of the Primary Efficacy Endpoint**		
Analysis population and time point description	Per-Protocol (PP) set The PP set consisted of all randomly assigned patients who received all full doses of study drug up to Week 4 (total 2 injections) and had a BCVA assessment at Week 8. A major protocol deviation that might have affected the interpretation of study results of primary efficacy endpoint led to exclusion from PP set. Patients were analysed according to the treatment group they were assigned to at randomization. **Week 8**		
Descriptive statistics and estimate variability	Treatment group	CT-P42	EU-approved Eylea
	Number of subjects	165	167

Title: A Randomized, Active-Controlled, Double-Masked, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P42 in Comparison with Eylea in Patients with Diabetic Macular Edema			
Study identifier	CT-P42 3.1 (protocol number), 2020-004278-23 (EudraCT Number)		
	Method: based on available cases LS Means (Standard Error) of change from baseline in BCVA at Week 8	9.22 (0.837)	8.84 (0.840)
	LS Mean difference (CT-P42 – Eylea) [95% CI]	0.38 [-0.90, 1.66]	

2.5.5.3. Clinical studies in special populations

Not applicable

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

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

Not applicable

2.5.5.6. Supportive study(ies)

Analysis of Usability

Usability was assessed to evaluate the ability of healthcare professionals to follow the instructions for use to prepare and administer the IVT injection to patients while maintaining aseptic conditions in the intended use environment, and to document any use errors on all tasks. Tasks specific to the unpacking, preparing, proper administration and disposal of the study drug were assessed by the study centre personnel. At the time of the usability assessment, injections were administered by investigators, assisted with the study drug preparation by assistants. The study centre personnel observed and evaluated the procedures for use errors and close calls on all tasks and completed the injection assessment checklist during the injection.

Usability was evaluated as a secondary objective in Study CT-P42 3.1.

The following secondary usability endpoints were assessed:

- Number of injections with vial kit successfully administered by healthcare professionals at Week 0
- Number of injections with PFS successfully administered by healthcare professionals at Extension Week 0

In the Main Study Period, usability assessments for vial kit of CT-P42 or Eylea were planned to be performed at Week 0 in approximately 60 patients (30 patients per treatment group) who were administered the study drug (CT-P42 or Eylea vial) at Week 0. In the Extension Study Period, usability assessments for CT-P42 PFS were planned to be performed at Extension Week 0 in approximately 30 patients who were scheduled to receive the study drug (CT-P42 PFS) at Extension Week 0.

The usability set for vial kit was defined as all patients in the safety set for the Main Study Period who had evaluable usability measurements at Week 0. The usability set for vial kit was used for the usability analysis of CT-P42 and Eylea vial kit.

The usability set for PFS was defined as all patients in the safety set for Extension Study Period who had evaluable usability measurements at Extension Week 0. The usability set for PFS was used for the usability analysis of CT-P42 PFS.

Usability assessment results were listed and tabulated for the usability set for vial kit and usability set for PFS, respectively.

All injections with vial kit at Week 0 were successfully administered without any use errors or close calls in both the CT-P42 group and Eylea group (45/45 and 50/50, respectively).

All injections with PFS at Extension Week 0 were successfully administered without any use errors or close calls (30/30).

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant conducted a single pivotal therapeutic similarity Phase III study in patients with diabetic macular oedema (DME). The study was not aimed at establishing efficacy per se, since efficacy in the respective therapeutic indications has already been established for the reference product Eylea. Instead, the study aimed at demonstrating similarity with respect to efficacy between the biosimilar candidate and the reference product.

Study CT-P42 3.1 was a randomized, active-controlled, double-masked, parallel-group, and multicentre Phase III study designed to evaluate the efficacy, PK, usability, and overall safety including immunogenicity of CT-P42 compared with EU-approved Eylea via IVT injection using a single-dose vial kit followed by a 4-week open-label, single-arm extension study to evaluate the usability, efficacy and safety of CT-P42 via IVT injection using a PFS in patients with DME.

Overall, the design of the pivotal Phase III study was considered adequate and generally in line with previous EMA scientific advices. In particular, the CHMP recommended a design that allowed follow up of sufficient number of patients in both treatment groups for one year to compare the efficacy, safety and immunogenicity of the proposed biosimilar to aflibercept (EMEA/H/SA/4380/1/2020/III). The study design was modified to provide sufficient long-term data for the control group (Eylea) to compare with CT-P42, which is acknowledged. This study consists of a screening period, the Main Study Period of 52 weeks and an Extension Study Period of 4 weeks. The duration of the study is therefore considered adequate to assess whether the initially observed similarity in clinical efficacy is maintained for at least one year.

Study population

The study was conducted in male and female subjects aged ≥18 years with DME secondary to type 1 or type 2 diabetes involving the centre of the macula in the study eye. DME is one of the approved indications of Eylea in the EU. Other approved indications include neovascular age-related macular degeneration (nAMD), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to DME, and visual impairment due to myopic choroidal neovascularisation (myopic CNV). Neovascular AMD (nAMD) and DME are likely the most sensitive indications compared to RVO, and CNV to detect possibly existing differences between the treatments.

Although the largest treatment effect can generally be anticipated in patients with nAMD, it is agreed that DME can be considered sufficiently sensitive based on literature supporting potentially lower variability in patients with DME compared to nAMD.

Binding to VEGF-A and PlGF is considered the main mechanism of action of aflibercept across different ophthalmological indications approved for the reference product and aflibercept is directly delivered at its site of action. Further, the safety and immunogenicity of aflibercept in DME are considered representative for the other indications. Thus, DME patients can generally be considered a sensitive population for assessing similarity in clinical efficacy of aflibercept, and it is agreed that, if similarity is demonstrated in DME patients, the findings can be extrapolated to other indications approved for Eylea (nAMD, CRVO/BRVO, DME and myopic CNV).

The inclusion criterion for BCVA score was 73 to 34 (approximate Snellen equivalent of 20/40 to 20/200) using ETRS charts and central subfield thickness (CST) of ≥350 µm as determined by OCT. Central subfield was defined as the circular region centred on the anatomic fovea with a radius of 500 microns. The lower BCVA limit (20/200) corresponds to the WHO defined level of legal blindness, while the upper limit (20/40) leaves enough room for 15 letter gain. The CST inclusion criterion of ≥350 µm was recommended in scientific advice to decrease subject variability and leave sufficient room for improvement. This was adopted by the applicant. Only DME patients with no prior exposure to previous systemic or ocular treatment with aflibercept and/or previous treatment with ocular anti-angiogenic agents in the study eye were included in the study. Treatment-experienced patients may have reached the plateau in terms of maximal gain in visual acuity which makes them a less sensitive population.

It is acknowledged that the applicant followed the CHMP recommendations and modified the inclusion/exclusion criteria to include a more homogenous population to increase sensitivity to detect possible differences between the biosimilar candidate and the originator with regard to BCVA baseline scores (73 to 34), myopia dioptres cut-off value (−6 dioptres), CST cut-off value (≥350 µm), HbA1c cut-off value (10%), evidence or suspicion of infection and previous anti-angiogenic and corticosteroid treatments (EMEA/H/SA/4380/1/2020/III and EMEA/H/SA/4380/1/FU/1/2020/II). Therefore, the inclusion and exclusion criteria were acceptable and in line with the scientific advice provided for the proposed study population and like other studies conducted for other biosimilar products.

Notably, the eligibility criteria were changed in the third global version of the protocol (14.1.2022) after the first subject had been assigned to treatment (22.7.2021). The applicant was asked to discuss the rationale for these changes and to present a summary on how many subjects had been enrolled in conflict with the former and the updated eligibility criteria. Based on the response, it was concluded, that no subjects were affected by this change.

Intervention

In the main study period, patients were administered either 2 mg/ 0.05ml CT-P42 or EU-sourced Eylea via IVT injection using a single dose-dose vial every 4 weeks for 5 doses (Weeks 0, 4, 8, 12, 16), then every 8 weeks for 4 doses (weeks 24, 32, 40, 48). In the extension study period one additional dose of CT-P42 was administered IVT via PFS at a recommended time of 8 weeks after week 42 in the main study period at the investigators discretion. This is in line with the posology approved for Eylea in DME.

This dosing regimen is recommended for DME patients in the SmPC of Eylea, which also states that "based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or individualized, such as with a treat-and-extend dosing regimen, where the treatment intervals are usually increased by 2-week increments to maintain stable visual and/or anatomic outcomes." However, flexible dosing was not considered reasonable in a trial aimed at evaluating biosimilarity and therefore, the chosen dosing regimen was considered acceptable to demonstrate clinical equivalence.

EU-sourced Eylea was used as the comparator in study CT-P42 3.1 which is preferred over reference medicinal products not authorized in the EEA.

The treatment duration in the main study period was 48 weeks, after which the last assessment was made at week 52. Following a 4 week pause, 31 patients from the main study period regardless of treatment were enrolled in the extension study period, during which one additional dose of CT-P42 was administered IVT via PFS. Main reason for this was the assessment of usability of the different administration devices.

Methods of assessment for primary and secondary efficacy

The methods used for the primary (best corrected visual acuity) and secondary efficacy assessments (SD-OCT, fundus photography and fluorescein angiography) represent standards used for the respective assessments.

Randomisation

Subjects were randomised in a 1:1 ratio to receive either CT-P42 or Eylea. No explicit information on the method to generate the random allocation sequence was given but the provided randomization list specifies block sizes of 2 and 4, which suggests that permuted block randomization with varying block size was used, which was considered adequate.

Blinding

The study was conducted in a double-masked manner during the Main Study Period and in an open-label manner during the Extension Study Period. A preliminary CSR was prepared by predefined unmasked personnel from Sponsor and CRO when the data up to Week 24 were available for each patient. The randomization codes for the Main Study Period were not to be revealed to study patients, investigators and study centre personnel until the final CSR had been generated. The masking strategy was considered suitable.

Primary endpoint

The primary objective of this study was to demonstrate the equivalence in efficacy of CT-P42 compared to Eylea in subjects with DME. The primary endpoint "change from baseline in BCVA using the ETDRS chart at Week 8" was considered appropriate for this objective. Change from baseline in BCVA is a continuous endpoint which can detect improvement or deterioration in the disease status and was considered to be a sensitive endpoint to detect differences between the biosimilar candidate and the reference product.

Week 8 was considered as a sensitive time point to detect differences between CT-P42 and Eylea in terms of BCVA change from baseline, as it corresponds to the ascending part of the time/response curve, before the efficacy plateau is reached.

Equivalence between the main treatment groups was to be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The pre-defined equivalence margin was also acceptable, since ± 3 letters are likely of low or no clinical relevance.

The applicant has justified this equivalence margin based on the results of the meta-analysis of the two randomized controlled studies for the reference product in DME patients (VIVID and VISTA studies), in which the lower bound of effectiveness was 4.1 letters, and has further adjusted it to ± 3 letters to ensure an adequate clinically meaningful equivalence margin, which is endorsed. Furthermore, the ± 3 letters equivalence margin has been used in the development of another aflibercept biosimilar authorised in the EU (EPAR Yesafili, EMEA/H/C/006022).

Estimands

The protocol did not define an explicit estimand and the primary analysis is not compliant with the estimand framework. The primary efficacy analysis was conducted on the FAS excluding the 7 patients with missing information on the primary endpoint change in BCVA from baseline to week 8. Thus, potential intercurrent events such as adverse events leading to treatment discontinuation, were either handled by the treatment policy strategy if the patients came in for the week 8 BCVA assessment or by exclusion of the corresponding patients if they missed the week 8 BCVA assessment. Considering the limited number of affected subjects, the clear results supporting biosimilarity and the provided sensitivity analysis, the presented primary analysis was considered acceptable to permit a conclusion on clinical biosimilarity.

Secondary efficacy endpoints

The secondary objective of this study was to evaluate additional efficacy, pharmacokinetics (PK), usability, and overall safety including immunogenicity. With regard to efficacy, continuous as well as responder analyses (losses and gains) of BCVA, as well as mean change in CST from baseline were assessed at weeks 1, 4, 8, 12, 16, 24, 32, 40 and 52/EOS1, as recommended by the CHMP Scientific Advice to cover the time-response curve over a longer period (including earlier and later time-points) compared to the primary endpoint, to further strengthen the evidence for biosimilarity). The proportion of patients with a ≥2-step improvement from baseline in the ETDRS DRSS Score was assessed at weeks 8, 24 and 52/EOS1, which is also endorsed.

Statistical methods

Definition of the analysis sets was acceptable.

Assessment of clinical similarity was based on the two-sided 95% confidence interval for the difference in mean change from baseline BCVA at week 8, estimated from an ANCOVA adjusted for baseline BCVA and country. In the protocol, the FAS is declared as the primary analysis population which is in contradiction with the fact that patients with missing information on the primary efficacy endpoint were to be excluded from the analysis (as finally implemented in the analysis and implicitly predefined in the SAP by defining a sensitivity analysis 'evaluating the impact of missing data on the primary efficacy endpoint results'). Thus, the primary analysis population was effectively the FAS excluding patients with missing information on the primary efficacy endpoint, which is not in line with the estimand framework and could lead to biased results if the pattern of missingness was different between the groups. Given the limited number of subjects with missing information on the primary endpoint and the performed sensitivity analysis using multiple imputation under the MAR assumption, no

further analyses are requested. However, the applicant is asked to clarify whether the analysis set used for the primary analysis was indeed the FAS excluding patients with missing information on the primary outcome.

The SAP left open, whether the categories of the adjustment variable 'country' were to be pooled (Europe vs. Non-Europe) in the analysis of the primary endpoint. The presented analyses were based on the information from the electronic case report forms, i.e. using the variable 'country' without pooling. As there was only one Lithuanian patient and two Estonian patients in the ITT set, it might have been more reasonable to use the pooled variable. However, the requested analyses based on the pooled variable 'country' gave similar results to the analyses without pooling with 95% confidence intervals contained well within the acceptance range of (-3, 3) letters.

The planned subgroup analyses are considered adequate.

The sample size calculation can be followed from the technical perspective. There was one update of the sample size calculation when the study was already ongoing. As the update was not informed by preliminary study data but mainly motivated by the publication of study results for the reference product, no concerns are raised.

The second version of the statistical analysis plan was finalized after the data base lock, but changes compared to the first version mainly pertain to the presentation of results for the extension study period and are considered of minor relevance.

The main conclusion regarding clinical similarity was based on the two-sided 95% confidence interval for the between group difference in mean change from baseline BCVA at Week 8. This is in line with established requirements for the demonstration of biosimilarity and considered adequate. Analyses of secondary endpoints and subgroup analyses were not controlled for multiplicity. This was considered acceptable as no corresponding secondary claims were intended.

Efficacy data and additional analyses

Participant flow and protocol deviations

Of a total of 484 screened subjects, 136 patients were excluded from the study due to screening failures. The most frequently reported primary reason for screening failure was inclusion/exclusion criteria not met (119 patients). A total of 348 subjects were randomised and received study treatment (173 in the CT-P42 group and 175 in the Eylea group). A total of 306 (87.9%) patients completed the Main Study Period (153 [88.4%] patients in the CT-P42 group and 153 [87.4%] patients in the Eylea group). The rate of early study discontinuation during the Main Study Period was similar across treatment groups (CT-P42: 11.6%; Eylea: 12.6%). The most frequently reported primary reasons for study discontinuation were withdrawal by patient (4.6% and 3.4%, respectively) and adverse event (3.5% and 4.0%, respectively). A total of 31 patients were enrolled in the single-arm Extension Study Period (PFS CT-P42). None of the patients discontinued the study prematurely during the Extension Study Period.

The main study period had a completion rate of 88.4% and 87.4% for CT-P42 and Eylea respectively. 169 patients in the CT-P42 group and 172 patients in the Eylea group completed the week 8 visit for primary efficacy analysis. All subjects in the extension study completed this period. The participant flow does not give rise to concerns.

3 cases of major protocol deviations due to non-adherence to I/E criteria were reported in each study group and additionally, one patient in the Eylea group received prohibited medication (Ranibizumab in the fellow eye for the treatment of DME at week 0). According to the applicant, patients with major protocol deviations were

excluded from the PP set. However, uncertainty remains for major protocol deviations related to OCT at baseline as discussed further below.

Due to the COVID-19 pandemic, the most frequently reported deviation was "Out of Visit Window" in 7 patients (6 [3.5%] patients in the CT-P42 group and 1 [0.6%] patient in the Eylea group) and "Visit Missing" in 3 patients (1 [0.6%] patients in the CT-P42 group and 2 [1.1%] patients in the Eylea group). Two patients did not have the BCVA score at the Week 8 visit. Due to the War in Ukraine, the most frequently reported deviation was "Use Local Laboratory" (7 [4.0%] patients in the CT-P42 group and 10 [5.7%] patients in the Eylea group), followed by "Missing 1 or More Examination at Study Visit" (5 [2.9%] patients in the CT-P42 group and 6 [3.4%] patients in the Eylea group) and "Out of Visit Window" (2 [1.2%] patients in the CT-P42 group and 3 [1.7%] patients in the Eylea group). Protocol deviations due to the COVID-19 pandemic and the war in Ukraine were not considered as a major protocol deviation.

In summary, the protocol deviations between the study groups were overall similar and are not considered concerning.

All of the 348 randomized patients (ITT set) were included in the FAS and 332 patients were included in the PP set. It is understood that the primary analysis set was the FAS excluding patients with missing values for the primary endpoint. The PP set was used for a supportive analysis of the primary endpoint.

Baseline data

Overall, the number of subjects was well balanced for the Main study period. Randomization was stratified for country, BCVA score on Day 1 [<55 letters vs. ≥55 letters] and PK subgroup [yes vs. no].

Demographic characteristics were comparable between the study groups. The mean age was 62.7 years [range: 25 - 86] and 58.3% of subjects were male. Most female subjects were not considered of child-bearing potential (95.9%). Subjects were largely white (mean: 64.4%), the remaining subjects were Asian (mean: 35.6%), and non-Hispanic or non-Latino (95.1). Most subjects were Never smokers (70.4%). The average screening height was 166.25cm (range: 145.0-197.0) and average screening weight was 77.55 kg (range: 39.93 – 147.0 kg). HbA1c at baseline was recorded as ≤8% (65.8%) and >8% (33.6 %). Patients from 12 countries were enrolled. At baseline, the majority of patients had a BCVA score of ≥55 letters (72.7%). 6.9% of patients from both groups were included in the PK subgroup.

Overall, the study population reflects the intended condition in the EU. In addition, the reported demographics appear balanced with only minor differences across treatment groups that do not give rise to concern.

For baseline disease characteristics the mean baseline BCVA letter score of patients in the main study period was 60.3 (range: 34 - 73) in the CT-P42 group and 60.4 (range: 34 – 73) in the Eylea group. The majority of patients had an ETDRS DRSS score of level 33.9 in both treatment groups (33.5% patients in the CT-P42 group and 34.3% patients in the Eylea group) and there was a similar percentage of patients in the ETDRS DRSS score at baseline between the 2 treatment groups. The mean (SD) CTS was higher by 15.6 µm in the CT-P42 group (499.3 [138.0] µm) than in the Eylea group (483.7 [111.5] µm), which might have contributed to different efficacy findings, as discussed in the next section. The mean (SD) IOP at baseline was similar between the 2 treatment groups (16.0 (2.8) mmHg in the CT-P42 group and 15.8 (2.7) mmHg in the Eylea group).

Baseline ocular characteristics in the study eye, as well as diabetes mellitus and DME history were similar across treatment groups, although the following differences are noted: DME was unilateral in 28.9% and 20.0% of the patients in the CT-P42 and Eylea groups, respectively, and CST at baseline was 499.3 µm and 483.7 µm for the CT-P42 and Eylea groups, respectively.

During the extension study period the median age was 64.7 years (range: 32-81). The majority of patients was male (58.3%) and all female patients in the extension period were designated not of childbearing potential. 100% of patients in the extension period were White, 6.5% of patients were Hispanic or Latino. Most subjects were Never smokers (54.8 %). The average height was 169 cm (range: 145.0-185.0) and average weight was 82.93 kg (range: 80.00 – 122.0 kg). HbA1c was ≤8% for 51.6% of subjects.

Primary endpoint

In the FAS, the observed LS mean change for BCVA at week 8 was similar between the CT-P42 and Eylea groups (9.43 letters and 8.85 letters respectively). The 95% CI of (-0.73, 1.88) for the treatment difference in BCVA at week 8 was entirely within the pre-defined equivalence margin of ±3 letters.

In the PP set the observed LS mean change for BCVA at week 8 was similar between the CT-P42 and Eylea groups (9.22 letters and 8.84 letters respectively). The 95% CI of (-0.90, 1.66) for the treatment difference was entirely within the equivalence margin of ±3 letters.

A sensitivity analysis was performed to assess the impact of missing data on the primary analysis by using multiple imputation with the missing at random assumption in the FAS. The results from the sensitivity analysis were similar to the results from the primary analysis using the FAS (treatment difference of 0.6 letters) and the 95% CI of (-0.70, 1.90) for the treatment difference was entirely within the equivalence margin of ±3 letters.

Overall, the primary analysis supports biosimilarity of CT-P42 and Eylea.

Secondary endpoints

The **mean changes in BCVA** were similar between the treatment groups at all time points. Baseline BCVA was well balanced between the groups and both CT-P42 and Eylea showed a consistent increase in BCVA up to week 16 and then stabilized with gradual improvements up to week 52. At baseline, the mean BCVA (± SD) was 60.3 (± 9.7) and 60.4 (± 10.1) in the CT-P42 and Eylea groups respectively. The mean (± SD) BCVA change from baseline at end of study was 12.1 ± 8.9 letters for CT-P42 (range: -38, 33) and 11.1 ± 9.9 letters for Eylea (range: -46, 35).

Up to week 24 the mean changes in BCVA were well comparable between the treatment groups, with only small deviations starting at week 32, which are considered negligible. The results from the investigation of mean change in BCVA from baseline support the biosimilarity of CT-P42 and Eylea.

The BCVA changes demonstrated in the main-study period were maintained in the extension period. At week 0 of the extension period, mean (± SD) BCVA was 72.4 (± 10.2) and at week 4 of the extension period (EOS2) mean BCVA was 72.3 (± 10.2).

Overall, the **proportion of patients with gained and lost ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA** was largely similar between the treatment groups from Week 1 - Week 8. However, at week 8, 76.9% of patients in the CT-P42 group had gained ≥5 letters, while the same change was only observed in 68.0% of patients in the Eylea group. The proportions of patients who gained ≥10, and ≥15 letters were nearly identical.

The proportions of patients with gained and lost ≥5, ≥10, and ≥15 ETDRS letters from Week 12 – Week 52 remained overall quite consistent between the treatment groups. A consistently higher response percentage in the proportion of patients who gained ≥5 letters when treated with CT-P42 compared to Eylea, of ~6% was observed.

At week 8, 76.9% of patients in the CT-P42 group had gained ≥5 letters, while the same change was only observed in 68.0% of patients in the Eylea group. The applicant was asked to discuss the clinical relevance of the observed difference between groups as well as the consistent trend in 6% higher response in the CT-P42 group in the proportion of patients who had a gain of ≥5 letters from week 12 to week 52/EOS1. The applicant argued that the difference in ≥5 letter-gain at week 8 might be a random finding caused by dichotomization of the continuous endpoint change in BCVA. This is supported by a similar proportion of patients having ≥3, and ≥4 letter gain, while the difference is only visible in the ≥5 letter gain group. At week 8, a larger number of patients showed a 4 letter gain in ETDRS in the Eylea group (n = 18) compared to the CT-P42 group (n = 8). At the subsequent time points, this measured difference shrank in size. Of note, the numbers of patients showing improvements of ≥10 letters and ≥15 letters were generally similar between treatment arms during the study period. Therefore, this finding is indeed considered random and does not indicate dissimilarity.

Patients in the extension period had a slightly higher starting response proportion in ≥5, ≥10, and ≥15 ETDRS letter gain from baseline than patients at the end of the main study period. A slight decrease in all categories was observed at extension week 4.

The applicant evaluated changes in **central subfield retinal thickness** (CST) from baseline between the CT-P42 and Eylea treatment groups as assessed via SD-OCT. The same device was used on a patient level throughout the study. If a switch was inevitable, the switched device type was used for the remainder of the study. Overall, 11 subjects were affected by the switch (6 [3.5%] and 5 [2.9%] in the CT-P42 and Eylea groups, respectively) and the proportion of subjects affected was similar between the treatment groups.

The mean change from baseline in CST in the CT-P42 group consistently showed greater absolute decrease than in the Eylea group at all assessed time points, although improvements were present in both groups. At week 8, change in CST was assessed in 167 patients in the CT-P42 group and 169 patients in the Eylea group (FAS). A mean (±SD) change from baseline of -169.2 ± 152.2 µm and -131.2 ± 113.7 µm were observed in the CT-P42 and Eylea groups, respectively. CST remained largely stable in both groups between week 16 and 40 and showed improvements from visit at week 48 to week 52. At week 52, the CT-P42 group showed a mean (±SD) change in CST of -220.7 ± 147.1 µm, while the Eylea group showed a mean (±SD) change in CST of -191.2 ± 137.0 µm.

Notably, there were two relevant differences between the treatment groups that potentially influenced results: the CT-P42 group had higher average CST values at baseline (499.3 µm ± 138.0 µm vs. 483.7 µm ± 111.5 µm), although the median was similar (465.5 µm and 462.5 µm for CT-P42 and Eylea respectively); and there was a higher proportion of patients with subretinal fluid within 500 µm of the macular centre in the CT-P42 group compared to the EU-approved Eylea group (47.4% (82/173) and 36.0% (63/175) of patients, respectively). The applicant argues that this could have led to differences in treatment response. The applicant was asked to calculate differences with 95% confidence intervals in change of CST from baseline between CT-P42 and Eylea for all timepoints (weeks 1, 4, 8, 12, 16, 24, 32, 40, 48 and 52) and provide differences adjusted for baseline CST value and country by applying Analysis of Covariance models with change in CST from baseline to the respective study week as dependent variable and country, baseline CST value and treatment group as independent variables and discuss the results with regards to clinical relevance.

Based on the submitted response it was determined that without adjustment, the estimated treatment difference ranged from -16.7 µm to -38.04 µm for CT-P42 vs. Eylea, and with adjustment for baseline CST value, country and treatment group, the estimated treatment difference ranged from -5.58 µm to -29.79 µm and was closer to zero at all time points compared to the unadjusted analysis. These results suggest that part of the differences observed for the change in CST values can be explained by differences in baseline CST between the treatment arms, which is reassuring. Thus, although there is a consistent trend in numerically

larger CST reduction in the CT-P42 group compared to Eylea, it is agreed that the remaining unexplained difference is not clinically relevant, and also the primary endpoint supports similarity.

The proportions of patients with **≥2-step improvement from baseline in ETDRS DRSS** showed similar improvements between the two treatment groups at week 8, 24, and 56 in the FAS and PP set.

Subgroup and post-hoc analyses

The applicant performed subgroup analyses for change in BCVA from baseline at week 8 by the following subgroup characteristics: ADA positive subgroup or ADA negative subgroup, Age (< 65 or ≥ 65), sex (male or female), race (Asian or White), baseline HbA1c (≤ 8 % or > 8 %), and baseline BCVA (< 40 letters, ≥ 40 to < 55 letters, ≥ 55 to < 65 letters, ≥ 65 letters).

Overall, similar efficacy results were observed in the different subgroups. Due to the small number of patients with ADAs at week 8 (3 and 2 for CT-P42 and Eylea respectively), potential influences on efficacy cannot be assessed. The occurrence of ADAs was low over the entirety of the study period and no further analyses are considered necessary.

The baseline BCVA <40 letters subgroup with 9 and 6 participants in the CT-P42 and Eylea subgroup respectively showed an average difference in BCVA change from baseline of 5.3 letters. Due to the size of the subgroup and the large standard deviation, this is not considered concerning. This also applies for the subgroups ≥ 40 to < 55 letters and ≥ 55 to < 65 letters, where patients receiving CT-P42 showed slightly larger average change from baseline compared to Eylea.

For the FAS, the results of mean (± SD) change from baseline of BCVA in the study eye at week 8 were 8.5 ± 6.3 letters in the CT P42 group and 8.2 ± 6.2 letters in the EU-approved Eylea group when excluding fellow-eye treated patients, which was very similar to the values observed for all patients in the treatment groups irrespective of whether fellow eye was treated or not.

The results of the post-hoc analysis indicate that fellow eye treatment does not affect efficacy in the study eye.

Usability

The ability of healthcare professionals to follow the instructions for use to successfully prepare and administer the IVT injection to patients was evaluated in the Extension Period of Study CT-P42 3.1. The results demonstrate that intravitreal administration can be achieved successfully with both, the vial and the PFS presentation.

2.5.7. Conclusions on the clinical efficacy

From an efficacy perspective, the clinical data indicate similarity between the proposed biosimilar Eydenzelt (CT-P42) and the reference product EU-approved Eylea.

2.5.8. Clinical safety

The safety information is based on the single clinical Study CT-P42 3.1 in DME patients with Main Study Period data up to Week 52 and Extension Study Period data up to Extension Week 4 for each patient. From 22 July 2021 (first patient randomly assigned to treatment) to 24 April 2023 (last patient Week 52 visit), safety data for 348 patients in Main Study Period and 31 patients in Extension Study Period are available.

The Safety Set for Main Study Period is defined as all randomly assigned patients who received at least 1 full or partial dose of study drug in Main Study Period. Patients were analysed based on the treatment actually received. The Safety Set for Main Study Period was the primary analysis set for the summary of safety data.

2.5.8.1. Patient exposure

348 patients with DME received 2 mg/0.05mL of CT-P42 or EU-approved Eylea IVT injection every 4 weeks for 5 doses, and, then every 8 weeks for 4 doses. Of these, 174 patients each were exposed to CT-P42 and EU-approved Eylea, respectively. One patient who was randomly assigned to the EU-approved Eylea group was administered CT-P42 at the Week 40 visit due to error in dispensation of kit by site staff. This patient was grouped as CT-P42 group for the Safety Set for Main Study Period according to the CT-P42 3.1 SAP V2.0.

Table 23: Number of patients who received the study drug (CT-P42, EU-approved Eylea) in study CT-P42 3.1 (safety set for main study period)

Dose Administered	Number of Subjects Who Received the Study Drug	
	CT-P42 (N=174)	EU-approved Eylea (N=174)
Week 0	174 (100%)	174 (100%)
Week 4	172 (98.9%)	171 (98.3%)
Week 8	170 (97.7%)	168 (96.6%)
Week 12	167 (96.0%)	163 (93.7%)
Week 16	166 (95.4%)	164 (94.3%)
Week 24	163 (93.7%)	161 (92.5%)
Week 32	159 (91.4%)	157 (90.2%)
Week 40	156 (89.7%)	152 (87.4%)
Week 48	154 (88.5%)	152 (87.4%)
Total Number of Doses Received		
n	174	174
Mean (SD)	8.5 (1.4)	8.4 (1.6)
Median	9.0	9.0
Min, Max	2, 9	1, 9

After the completion of Main Study Period, 31 patients with DME (15 and 16 patients in the CT-P42 and EU-approved Eylea groups, respectively in Main Study Period) entered into Extension Study Period for evaluation of PFS usability. Thirty patients received 1 dose of CT-P42 PFS and 1 patient wrongly received CT-P42 vial at Extension Week 0. All of them are included in the Safety Set for Extension Study Period in accordance with the definition of the analysis set, all patients who received a full or partial dose of study drug in Extension Study Period. The Safety Set for Extension Study Period was used for the analysis of all safety and efficacy data collected on or after Extension Week 0. In this submission, safety results up to Extension Week 4/EOS2 visit from Safety Set for Extension Study Period from 31 patients with DME in Study CT-P42 3.1 are included.

2.5.8.2. Adverse events

The following table gives an overview of treatment-emergent AEs (TEAEs) in Study CT-P42 3.1.

Table 24: Overview of TEAEs in study CT-P42 3.1 in DME patients (safety set for main study period)

	CT-P42 (N=174)	EU-approved Eylea (N=174)
Total number of TEAEs, n	269	318
Number (%) of patients with ≥ 1 TEAE	109 (62.6%)	117 (67.2%)
Related	8 (4.6%)	6 (3.4%)
Unrelated	107 (61.5%)	115 (66.1%)
Number (%) of patients with ≥ 1 TESAE	19 (10.9%)	17 (9.8%)
Related	1 (0.6%)	1 (0.6%)
Unrelated	18 (10.3%)	16 (9.2%)
Number (%) of patients with ≥ 1 TEAE leading to discontinuation of study drug	6 (3.4%)	6 (3.4%)
Related	1 (0.6%)	1 (0.6%)
Unrelated	5 (2.9%)	5 (2.9%)
Number (%) of patients with ≥ 1 TEAE classified as potential ATE	8 (4.6%)	8 (4.6%)
Related	1 (0.6%)	1 (0.6%)
Unrelated	7 (4.0%)	7 (4.0%)
Number (%) of patients with ≥ 1 TEAE related to injection procedure	7 (4.0%)	16 (9.2%)
Related	2 (1.1%)	3 (1.7%)
Unrelated	6 (3.4%)	13 (7.5%)
Number (%) of TEAE leading to Death	3 (1.7%)	2 (1.1%)
Related	0	0
Unrelated	3 (1.7%)	2 (1.1%)
Total number of ocular TEAEs in the study eye, n	48	61
Number (%) of patients with ≥ 1 TEAE in the study eye	31 (17.8%)	38 (21.8%)
Related	7 (4.0%)	4 (2.3%)
Unrelated	25 (14.4%)	34 (19.5%)
Number (%) of patients with ≥ 1 TESAE in the study eye	0	0
Number (%) of patients with ≥ 1 TEAE in the study eye leading to discontinuation of study drug	1 (0.6%)	1 (0.6%)
Related	1 (0.6%)	0
Unrelated	0	1 (0.6%)
Number (%) of patients with ≥ 1 TEAE in the study eye classified as potential ATE	0	0

Number (%) of patients with ≥ 1 TEAE in the study eye related to injection procedure	7 (4.0%)	15 (8.6%)
Related	2 (1.1%)	3 (1.7%)
Unrelated	6 (3.4%)	12 (6.9%)
Number (%) of TEAE in the study eye leading to Death	0	0
Total number of ocular TEAEs in the fellow eye, n	47	55
Number (%) of patients with ≥ 1 TEAE in the fellow eye	37 (21.3%)	45 (25.9%)
Related	0	0
Unrelated	37 (21.3%)	45 (25.9%)
Number (%) of patients with ≥ 1 TESAE in the fellow eye	0	0
Number (%) of patients with ≥ 1 TEAE in the fellow eye leading to discontinuation of study drug	0	0
Number (%) of patients with ≥ 1 TEAE in the fellow eye classified as potential ATE	0	0
Number (%) of patients with ≥ 1 TEAE in the fellow eye related to injection procedure	0	2 (1.1%)
Related	0	0
Unrelated	0	2 (1.1%)
Number (%) of TEAE in the fellow eye leading to Death	0	0
Total number of non-ocular TEAEs, n	178	214
Number (%) of patients with ≥ 1 non-ocular TEAE	86 (49.4%)	93 (53.4%)
Related	1 (0.6%)	3 (1.7%)
Unrelated	86 (49.4%)	93 (53.4%)
Number (%) of patients with ≥ 1 non-ocular TESAE	19 (10.9%)	17 (9.8%)
Related	1 (0.6%)	1 (0.6%)
Unrelated	18 (10.3%)	16 (9.2%)
Number (%) of patients with ≥ 1 non-ocular TEAE leading to discontinuation of study drug	5 (2.9%)	5 (2.9%)
Related	0	1 (0.6%)
Unrelated	5 (2.9%)	4 (2.3%)
Number (%) of patients with ≥ 1 non-ocular TEAE classified as potential ATE	8 (4.6%)	8 (4.6%)
Related	1 (0.6%)	1 (0.6%)
Unrelated	7 (4.0%)	7 (4.0%)
Number (%) of patients with ≥ 1 non-ocular TEAE related to Injection Procedure	0	1 (0.6%)
Related	0	0
Unrelated	0	1 (0.6%)
Number (%) of non-ocular TEAE leading to Death	3 (1.7%)	2 (1.1%)

Related	0	0
Unrelated	3 (1.7%)	2 (1.1%)

Note: The total number of TEAEs counted includes events for all patients in the Safety Set for Main Study Period.
Abbreviations: ATE, arterial thromboembolic event; N, number of patients in the respective group; n, number of patients within a specific category; SAE, serious adverse event

Overall, the number/proportion of patients who experienced at least 1 TEAE was 109 [62.6%] and 117 [67.2%] patients in the CT-P42 and EU-approved Eylea groups, respectively. The most frequently reported TEAE by system organ class (SOC) was eye disorders (51 [29.3%] and 59 [33.9%] patients, respectively) and by preferred term (PT) was diabetic retinal oedema (17 [9.8%] and 23 [13.2%] patients, respectively). In addition, ocular TEAEs in the study eye, ocular TEAEs in the fellow eye, and non-ocular TEAEs were similar between the treatment groups.

Only 3 (9.7%) patients who received CT-P42 PFS experienced at least 1 TEAE for Extension Study Period in Study CT-P42 3.1. All TEAEs were considered to be unrelated to the study drug and most cases were reported as non-ocular TEAEs. None of ocular TEAEs were reported in the study eye and all TEAEs were reported as non-ocular TEAEs except 1 ocular TEAE in the fellow eye.

Ocular TEAE in the Study Eye

Main Study Period

The number/proportion of patients who experienced at least 1 ocular TEAE in the study eye was 31 [17.8%] and 38 [21.8%] patients in the CT-P42 and EU-approved Eylea groups, respectively. Ocular TEAEs in the study eye reported for at least 1% patients in any treatment group by PT are summarized in the following table. The most frequently reported ocular TEAE by PT in the study eye was intraocular pressure increased (3 [1.7%] and 4 [2.3%] patients, respectively), followed by conjunctival haemorrhage (2 [1.1%] and 4 [2.3%] patients, respectively).

Table 25: Ocular TEAEs in the study eye reported for at least 1% of patients in any treatment group by PT in study CT-P42 3.1 (safety set for main study period)

System Organ Class (SOC) Preferred Term (PT)	**CT-P42 (N=174)**	**EU-approved Eylea (N=174)**
Total number of ocular TEAEs in the study eye, n	**48**	**61**
Total number of patients with ≥ 1 ocular TEAE in the study eye, n (%)	**31 (17.8%)**	**38 (21.8%)**
Eye disorders	**21 (12.1%)**	**26 (14.9%)**
Cataract	3 (1.7%)	2 (1.1%)
Cataract nuclear	0	2 (1.1%)
Cataract subcapsular	1 (0.6%)	2 (1.1%)
Conjunctival haemorrhage	2 (1.1%)	4 (2.3%)
Corneal erosion	2 (1.1%)	0

Dry eye	0	3 (1.7%)
Epiretinal membrane	1 (0.6%)	2 (1.1%)
Eye pain	1 (0.6%)	3 (1.7%)
Eyelid irritation	1 (0.6%)	2 (1.1%)
Foreign body sensation in eyes	3 (1.7%)	1 (0.6%)
Ocular hypertension	0	2 (1.1%)
Posterior capsule opacification	2 (1.1%)	2 (1.1%)
Visual acuity reduced	1 (0.6%)	3 (1.7%)
Vitreous detachment	2 (1.1%)	1 (0.6%)
Vitreous floaters	3 (1.7%)	1 (0.6%)
Vitreous haemorrhage	3 (1.7%)	0
Infections and infestations	**2 (1.1%)**	**0**
Conjunctivitis	2 (1.1%)	0
Investigations	**3 (1.7%)**	**4 (2.3%)**
Intraocular pressure increased	3 (1.7%)	4 (2.3%)

Note: Only TEAEs reported for at least 1% of patients for Main Study Period in either treatment group were included.

Extension Study Period

There were no ocular TEAEs in the study eye reported after treatment with a single dose of CT-P42.

Ocular TEAE in the Fellow Eye

Main Study Period

The number/proportion of patients who experienced at least 1 ocular TEAE in the fellow eye was 37 [21.3%] and 45 [25.9%] patients in the CT-P42 and EU-approved Eylea groups, respectively. Ocular TEAEs in the fellow eye reported for at least 1% patients in any treatment group by PT are summarized in the following table. The most frequently reported ocular TEAE by PT in the fellow eye was diabetic retinal oedema (17 [9.8%] and 23 [13.2%] patients, respectively), followed by cataract (3 [1.7%] and 2 [1.1%] patients, respectively), epiretinal membrane (3 [1.7%] and 2 [1.1%] patients, respectively), and visual acuity reduced (4 [2.3%] and 1 [0.6%] patients, respectively).

Table 26: Ocular TEAEs in the fellow eye reported for at least 1% of patients in any treatment group by PT in study CT-P42 3.1 (safety set for main study period)

SOC PT	**CT-P42 (N=174)**	**EU-approved Eylea (N=174)**
Total number of ocular TEAEs in the fellow eye, n	**47**	**55**
Total number of patients with ≥ 1 ocular TEAE in the fellow eye, n (%)	**37 (21.3%)**	**45 (25.9%)**
Eye disorders	**31 (17.8%)**	**35 (20.1%)**
Cataract	3 (1.7%)	2 (1.1%)

Cataract nuclear	0	2 (1.1%)
Diabetic retinal oedema	17 (9.8%)	23 (13.2%)
Dry eye	0	2 (1.1%)
Epiretinal membrane	3 (1.7%)	2 (1.1%)
Eyelid irritation	0	2 (1.1%)
Posterior capsule opacification	3 (1.7%)	1 (0.6%)
Visual acuity reduced	4 (2.3%)	1 (0.6%)
Vitreous floaters	0	3 (1.7%)
Vitreous haemorrhage	2 (1.1%)	0
Infections and infestations	**2 (1.1%)**	**0**
Conjunctivitis	2 (1.1%)	0

Note: Only TEAEs reported for at least 1% of patients for Main Study Period in either treatment group were included.

Extension Study Period

Only 1 (3.2%) patient treated with single dose of CT P42 experienced ocular TEAE in the fellow eye by PT of diabetic retinal oedema.

Non-ocular TEAE

Main Study Period

The number/proportion of patients who experienced at least 1 non-ocular TEAE was 86 [49.4%] and 93 [53.4%] patients in the CT-P42 and EU-approved Eylea groups, respectively. The most frequently reported non-ocular TEAE by PT was hypertension (11 [6.3%] and 16 [9.2%] patients, respectively), followed by COVID-19 (8 [4.6%] and 10 [5.7%] patients, respectively).

Extension Study Period

Only 2 (6.5%) patients who were treated with single dose of CT-P42 experienced non-ocular TEAEs and all of TEAEs were grade 1 and recovering/recovered.

Treatment-Emergent Adverse Events by Intensity

Most patients experienced TEAEs with grade 1 or 2 in intensity. In the Main Study Period, the number (%) of patients who experienced at least 1 common terminology criteria for AE (CTCAE) grade 3 or higher TEAE was 40 (23.0%) and 41 (23.6%) patients in the CT-P42 and EU-approved Eylea groups, respectively. The most frequently reported grade 3 or higher TEAE by SOC was eye disorders (10 [5.7%] and 5 [2.9%] patients, respectively) and by PT was hypertension (2 [1.1%] and 4 [2.3%] patients, respectively).

There was no patient who experienced at least 1 CTCAE grade 3 or higher TEAE for Extension Study Period in Study CT-P42 3.1.

Ocular TEAE (grade 3 or higher) in the Study Eye

Main Study Period

The number (%) of patients who experienced at least 1 CTCAE grade 3 or higher ocular TEAE in the study eye was 5 (2.9%) and 3 (1.7%) patients in the CT-P42 and EU-approved Eylea groups, respectively. All these events were grade 3 in intensity and none of grade 4 and grade 5 ocular TEAEs in the study eye were reported.

Ocular TEAE (grade 3 or higher) in the Fellow Eye

Main Study Period

The proportion of patients who experienced at least 1 CTCAE grade 3 or higher ocular TEAE in the fellow eye was similar between the treatment groups (7 [4.0%] and 2 [1.1%] patients in the CT-P42 and EU-approved Eylea groups, respectively. All of these TEAEs were considered to be unrelated to the study drug.

One patient (0.6%) in the CT-P42 group experienced grade 4 ocular TEAE (cataract by PT) in the fellow eye and none of grade 5 ocular TEAEs in the fellow eye were reported in any treatment group.

Non-ocular TEAE (grade 3 or higher)

Main Study Period

The number (%) of patients who experienced at least 1 CTCAE grade 3 or higher non-ocular TEAE was 32 (18.4%) and 36 (20.7%) patients in the CT-P42 and EU-approved Eylea groups, respectively. The most frequently reported grade 3 non-ocular TEAE by PT was hypertension (2 [1.1%] and 4 [2.3%] patients, respectively), followed by anaemia (2 [1.1%] patients in each treatment group).

Table 27: Grade 3 or higher non-ocular TEAEs reported for at least 1% of patients in any treatment group by SOC and PT in study CT-P42 3.1 (safety set for main study period)

SOC PT	CT-P42 (N=174)	EU-approved Eylea (N=174)
Number of patients with ≥ 1 grade 3 or higher non-ocular TEAE, n (%)[1]	**32 (18.4%)**	**36 (20.7%)**
Grade 3	27 (15.5%)	32 (18.4%)
Grade 4	2 (1.1%)	2 (1.1%)
Grade 5	3 (1.7%)	2 (1.1%)
Blood and lymphatic system disorders	**2 (1.1%)**	**2 (1.1%)**
Anaemia – Grade 3, Unrelated	2 (1.1%)	2 (1.1%)
Cardiac disorders	**2 (1.1%)**	**4 (2.3%)**
Cardiac failure – Grade 3, Unrelated	1 (0.6%)	2 (1.1%)
Cardiac failure – Grade 4, Unrelated	0	1 (0.6%)
General disorders and administration site conditions	**0**	**2 (1.1%)**
Death – Grade 5, Unrelated	0	2 (1.1%)
Hepatobiliary disorders	**2 (1.1%)**	**0**
Cholecystitis – Grade 3, Unrelated	2 (1.1%)	0
Infections and infestations	**3 (1.7%)**	**5 (2.9%)**
Cellulitis – Grade 3, Unrelated	0	2 (1.1%)

Pneumonia – Grade 3, Unrelated	1 (0.6%)	1 (0.6%)
Pneumonia – Grade 5, Unrelated	1 (0.6%)	0
Metabolism and nutrition disorders	**2 (1.1%)**	**4 (2.3%)**
Hyperkalaemia – Grade 3, Unrelated	1 (0.6%)	2 (1.1%)
Hyperkalaemia – Grade 4, Unrelated	1 (0.6%)	0
Nervous system disorders	**1 (0.6%)**	**2 (1.1%)**
Carotid artery stenosis – Grade 3, Unrelated	1 (0.6%)	2 (1.1%)
Skin and subcutaneous tissue disorders	**3 (1.7%)**	**3 (1.7%)**
Diabetic foot – Grade 3, Unrelated	2 (1.1%)	1 (0.6%)
Diabetic ulcer – Grade 3, Unrelated	0	2 (1.1%)
Vascular disorders	**2 (1.1%)**	**4 (2.3%)**
Hypertension – Grade 3, Related	0	1 (0.6%)
Hypertension – Grade 3, Unrelated	2 (1.1%)	3 (1.7%)

Note: At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted.
[1] The number of patients with at least one grade 3 or higher TEAEs includes all patients who reported grade 3 or higher TEAE in the Safety Set for Main Study Period.

Grade 4 non-ocular TEAEs were reported for 2 (1.1%) patients in the CT-P42 and EU-approved Eylea groups, respectively, and grade 5 non-ocular TEAEs were reported for 3 (1.7%) and 2 (1.1%) patients, respectively. All of these TEAEs were unrelated to study drug.

Adverse drug reactions

Overall, the majority of TEAEs were not related to study drug. The number/proportion of patients who had at least 1 TEAE considered by investigator to be related to the study drug was 8 [4.6%] and 6 [3.4%] patients in the CT-P42 and EU-approved Eylea group, respectively in the Main Study Period.

Study drug related ocular TEAEs in the study eye were reported for 7 (4.0%) and 4 (2.3%) patients in the CT-P42 and EU-approved Eylea groups, respectively. None of ocular TEAEs in the fellow eye were considered by investigator to be related to the study drug. Study drug related non-ocular TEAEs were reported for 1 (0.6%) and 3 (1.7%) patients, respectively.

There was no patient who had at least 1 TEAE considered by investigator to be related to the study drug in the Extension Study Period.

Table 28: Treatment-emergent adverse events by relationship and intensity (safety set for main study period)

	CT-P42 (N=174)	Eylea (N=174)	Total (N=348)
Total Number of Treatment-Emergent Adverse Events (TEAEs)	269	318	587
Number of Patients with at Least One Treatment-Emergent Adverse Event	109 (62.6%)	117 (67.2%)	226 (64.9%)
Related	**8 (4.6%)**	**6 (3.4%)**	**14 (4.0%)**
Grade 1	3 (1.7%)	2 (1.1%)	5 (1.4%)
Grade 2	2 (1.1%)	1 (0.6%)	3 (0.9%)
Grade 3	3 (1.7%)	3 (1.7%)	6 (1.7%)
Unrelated	**107 (61.5%)**	**115 (66.1%)**	**222 (63.8%)**
Grade 1	24 (13.8%)	31 (17.8%)	55 (15.8%)
Grade 2	44 (25.3%)	46 (26.4%)	90 (25.9%)
Grade 3	33 (19.0%)	34 (19.5%)	67 (19.3%)
Grade 4	3 (1.7%)	2 (1.1%)	5 (1.4%)
Grade 5	3 (1.7%)	2 (1.1%)	5 (1.4%)

Note: The total number of TEAEs count includes events for all patients in the Safety set for Main Study Period. At each level of summarization, patients are counted once if they reported one or more events. Only the most severe event is counted. The event is considered to be related if the relationship is defined as 'Possible', 'Probable' and 'Definite'. The intensity is defined as Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening, 5 = Death.

The number (%) of patients who experienced at least 1 CTCAE grade 3 or higher ocular TEAE in the study eye was 5 (2.9%) and 3 (1.7%) patients in the CT-P42 and EU-approved Eylea groups, respectively. Of these events, 2 TEAEs by PT of epiretinal membrane and macular ischaemia each in the CT-P42 group were considered to be possibly related to the study drug.

Table 29: Grade 3 or higher ocular TEAEs with relationship in the study eye by SOC and PT in study CT-P42 3.1 (safety set for main study period)

SOC PT	CT-P42 (N=174)	EU-approved Eylea (N=174)
Number of patients with ≥ 1 grade 3 or higher ocular TEAE in the study eye, n (%)[1]	**5 (2.9%)**	**3 (1.7%)**
Grade 3	5 (2.9%)	3 (1.7%)
Eye disorders	**4 (2.3%)**	**3 (1.7%)**
Cataract – Grade 3, Unrelated	1 (0.6%)	0
Epiretinal membrane – Grade 3, Related	1 (0.6%)	0
Macular ischaemia – Grade 3, Related	1 (0.6%)	0
Retinal vein occlusion – Grade 3, Unrelated	0	1 (0.6%)
Ulcerative keratitis – Grade 3, Unrelated	0	1 (0.6%)
Visual acuity reduced – Grade 3, Unrelated	0	2 (1.1%)
Visual impairment – Grade 3, Unrelated	1 (0.6%)	0
Injury, poisoning and procedural complications	**1 (0.6%)**	**0**
Eye contusion – Grade 3, Unrelated	1 (0.6%)	0
Investigations	**1 (0.6%)**	**0**
Intraocular pressure increased – Grade 3, Unrelated	1 (0.6%)	0

Note: At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted.
[1] The number of patients with at least one grade 3 or higher TEAEs includes all patients who reported grade 3 or higher TEAE in the Safety Set for Main Study Period.

2.5.8.3. Serious adverse event/deaths/other significant events

Arterial thromboembolic events (ATEs) and TEAEs related to IVT injection procedure were considered AESIs by considering Eylea's safety profile and were closely monitored.

Arterial thromboembolic events

In each treatment group, 8 (4.6%) patients experienced at least 1 ATE with non-ocular events in Main Study Period. The most frequently reported TEAE classified as ATE was carotid artery stenosis (1 [0.6%] and 2 [1.1%] patients in the CT-P42 and EU-approved Eylea groups, respectively). All of the TEAEs classified as ATE were non-ocular TEAEs and considered to be unrelated to the study drug except 1 case (myocardial infarction, grade 3) in the CT-P42 group and 1 case (ischaemic stroke, grade 3) in the EU-approved Eylea group. Both events were also categorised as serious TEAE.

The event in the CT-P42 group occurred 4 days after the Week 8 dose administration and resolved after both medication and non-medication treatment. The event in the EU-approved Eylea group occurred 47 days after the Week 24 dose administration and resolved with sequelae (subject apathetic, weakened, with mobility difficulties) after medications treatments.

Table 30: TEAE classified as arterial thromboembolic events by relationship and intensity in study CT-P42 3.1 (safety set for main study period)

SOC PT	**CT-P42 (N=174)**	**EU-approved Eylea (N=174)**
Total number of ATEs, n	**8**	**10**
Number of patients with ≥ 1 ATE, n (%)	**8 (4.6%)**	**8 (4.6%)**
Related	1 (0.6%)	1 (0.6%)
Grade 3	1 (0.6%)	1 (0.6%)
Unrelated	7 (4.0%)	7 (4.0%)
Grade 1	0	1 (0.6%)
Grade 2	2 (1.1%)	0
Grade 3	2 (1.1%)	4 (2.3%)
Grade 5	3 (1.7%)	2 (1.1%)
SOC PT	**CT-P42 (N=174)**	**EU-approved Eylea (N=174)**
Cardiac disorders	**4 (2.3%)**	**1 (0.6%)**
Cardiac arrest – Grade 5, Unrelated	1 (0.6%)	0
Coronary artery disease – Grade 2, Unrelated	1 (0.6%)	0
Coronary artery disease – Grade 3, Unrelated	0	1 (0.6%)
Myocardial infarction – Grade 3, Related	1 (0.6%)	0

Myocardial infarction – Grade 2, Unrelated	1 (0.6%)	0
General disorders and administration site conditions	**0**	**2 (1.1%)**
Death – Grade 5, Unrelated	0	2 (1.1%)
Infections and infestations	**1 (0.6%)**	**0**
Pneumonia – Grade 5, Unrelated	1 (0.6%)	0
Investigations	**0**	**1 (0.6%)**
Blood creatine phosphokinase increased – Grade 1, Unrelated	0	1 (0.6%)
Nervous system disorders	**1 (0.6%)**	**3 (1.7%)**
Carotid artery stenosis – Grade 3, Unrelated	1 (0.6%)	2 (1.1%)
Cerebral infarction – Grade 3, Unrelated	0	1 (0.6%)
Ischaemic stroke – Grade 3, Related	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**1 (0.6%)**	**0**
Dyspnoea – Grade 5, Unrelated	1 (0.6%)	0
Vascular disorders	**1 (0.6%)**	**1 (0.6%)**
Peripheral arterial occlusive disease – Grade 3, Unrelated	1 (0.6%)	0
Peripheral artery occlusion – Grade 3, Unrelated	0	1 (0.6%)

Note: The total number of TEAEs counted included events classified as ATEs for all patients in the Safety Set for Main Study Period. At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted.

There was no patient who experienced at least 1 TEAE classified as ATE in Extension Study Period.

TEAEs related to IVT injection procedure

The proportion of patients who experienced at least 1 ocular TEAE related to IVT injection procedure in the study eye was similar in the CT-P42 group (7 [4.0%] patients) and EU-approved Eylea group (15 [8.6%] patients). Most of the events were unrelated with the study drug and the proportion of patients who experienced study drug related ocular events in the study eye was similar between the treatment groups (2 [1.1%] and 3 [1.7%] patients, respectively).

The most frequently reported ocular TEAEs related to IVT injection procedure in the study eye were conjunctival haemorrhage and intraocular pressure increased (1 [0.6%] and 4 [2.3%] patients in the CT-P42 and EU-approved Eylea groups, respectively for both term).

Table 31: Ocular TEAE in the study eye related to intravitreal injection procedure by relationship and intensity in study CT-P42 3.1 (safety set for main study period)

SOC PT	CT-P42 (N=174)	EU-approved Eylea (N=174)
Total number of ocular TEAEs related to IVT injection procedure in the study eye, n	**9**	**27**
Number of patients with ≥ 1 ocular TEAE related to IVT injection procedure in the study eye, n (%)	**7 (4.0%)**	**15 (8.6%)**
Related	2 (1.1%)	3 (1.7%)
Grade 1	1 (0.6%)	1 (0.6%)
Grade 2	1 (0.6%)	2 (1.1%)
Unrelated	6 (3.4%)	12 (6.9%)
Grade 1	6 (3.4%)	12 (6.9%)
Eye disorders	**6 (3.4%)**	**11 (6.3%)**
Conjunctival haemorrhage – Grade 2, Related	1 (0.6%)	0
Conjunctival haemorrhage – Grade 1, Unrelated	0	4 (2.3%)
Corneal erosion – Grade 1, Unrelated	1 (0.6%)	0
Eye irritation – Grade 1, Unrelated	1 (0.6%)	0
Eye pain – Grade 1, Unrelated	0	3 (1.7%)
Eyelid irritation – Grade 1, Unrelated	1 (0.6%)	2 (1.1%)
Foreign body sensation in eyes – Grade 1, Unrelated	1 (0.6%)	1 (0.6%)
Ocular hypertension – Grade 1, Unrelated	0	1 (0.6%)
Vitreous detachment – Grade 1, Unrelated	0	1 (0.6%)
Vitreous floaters – Grade 1, Unrelated	1 (0.6%)	0
Investigations	**1 (0.6%)**	**4 (2.3%)**
Intraocular pressure increased – Grade 1, Related	1 (0.6%)	1 (0.6%)
Intraocular pressure increased – Grade 2, Related	0	2 (1.1%)
Intraocular pressure increased – Grade 1, Unrelated	1 (0.6%)	1 (0.6%)

Note: The total number of TEAEs counted included events related to IVT injection procedure for all patients in the Safety Set for Main Study Period. At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted.

Three ocular TEAEs related to IVT injection procedure in the fellow eye were reported in 2 (1.1%) patients in the EU-approved Eylea group. The TEAEs including eyelid irritation (grade 1), vitreous floaters (grade 1), and intraocular pressure increased (grade 2) were considered to be unrelated to the study drug.

Only 1 non-ocular TEAE of hypertension (grade 3) related to IVT injection procedure was reported in 1 (0.6%) patient in the EU-approved Eylea group and this case was considered to be unrelated to the study drug.

There was no patient who experienced at least 1 TEAE related to IVT injection procedure in Extension Study Period.

Deaths

A total of 5 patients died due to TEAEs during the study (3 [1.7%] and 2 [1.1%] patients in the CT-P42 and EU-approved Eylea group, respectively). The following preferred terms were attributed to these patients: Dyspnoea, Cardiac Arrest and Pneumonia in the CT-P42 group; Death (unknown) and Death (unknown) in the Eylea group. None of the cases was regarded as related to study drug.

Other Serious Adverse Events

Overall, the proportion of patients who experienced at least 1 TESAE was similar between the treatment groups in Main Study Period (19 [10.9%] and 17 [9.8%] patients in the CT-P42 and EU-approved Eylea groups, respectively). All TESAEs were non-ocular TESAEs. The most frequently reported non-ocular TESAEs by PT were cardiac failure (1 [0.6%] and 2 [1.1%] patients, respectively) and diabetic foot (2 [1.1%] and 1 [0.6%] patients, respectively).

Of these events, only 1 grade 3 TESAE of myocardial infarction reported in the CT-P42 group and 1 grade 3 TESAE of ischaemic stroke reported in the EU-approved Eylea group were considered to be related to the study drug. Details are provided above under ATE. All other TESAEs were considered to be unrelated to the study drug.

Most patients experienced TESAEs with grade 2 or 3 in intensity. In Main Study Period, the number (%) of patients who experienced at least 1 grade 4 or higher TESAE was 4 (2.3%) patients in the CT-P42 and EU-approved Eylea groups each.

There was no patient who experienced at least 1 TESAE in Extension Study Period.

Table 32: Non-ocular TESAEs by SOC and PT in study CT-P42 3.1 (safety set for main study period)

SOC PT	CT-P42 (N=174)	EU-approved Eylea (N=174)
Number of patients with ≥ 1 non-ocular TESAE, n (%)	**19 (10.9%)**	**17 (9.8%)**
Blood and lymphatic system disorders	**0**	**1 (0.6%)**
Deficiency anaemia – Grade 3, Unrelated	0	1 (0.6%)
Cardiac disorders	**4 (2.3%)**	**4 (2.3%)**
Aortic valve stenosis – Grade 4, Unrelated	0	1 (0.6%)
Atrial fibrillation – Grade 2, Unrelated	0	1 (0.6%)
Atrioventricular block second degree – Grade 3, Unrelated	1 (0.6%)	1 (0.6%)
Cardiac arrest – Grade 5, Unrelated	1 (0.6%)	0
Cardiac failure – Grade 3, Unrelated	1 (0.6%)	1 (0.6%)
Cardiac failure – Grade 4, Unrelated	0	1 (0.6%)
Coronary artery disease – Grade 3, Unrelated	0	1 (0.6%)
Myocardial infarction – Grade 3, Related	1 (0.6%)	0
Ear and labyrinth disorders	**0**	**1 (0.6%)**

Deafness neurosensory – Grade 3, Unrelated	0	1 (0.6%)
Gastrointestinal disorders	**1 (0.6%)**	**1 (0.6%)**
Enterocolitis – Grade 3, Unrelated	0	1 (0.6%)
Umbilical hernia – Grade 3, Unrelated	1 (0.6%)	0
General disorders and administration site conditions	**0**	**2 (1.1%)**
Death – Grade 5, Unrelated	0	2 (1.1%)
Hepatobiliary disorders	**2 (1.1%)**	**0**
Cholecystitis – Grade 3, Unrelated	2 (1.1%)	0
Infections and infestations	**5 (2.9%)**	**4 (2.3%)**
Carbuncle – Grade 3, Unrelated	0	1 (0.6%)
Cellulitis – Grade 3, Unrelated	0	1 (0.6%)
COVID-19 pneumonia – Grade 3, Unrelated	1 (0.6%)	0
Device related infection – Grade 3, Unrelated	1 (0.6%)	0
Diabetic gangrene – Grade 3, Unrelated	1 (0.6%)	0
Emphysematous pyelonephritis – Grade 4, Unrelated	0	1 (0.6%)
Gastroenteritis – Grade 3, Unrelated	1 (0.6%)	0
Pneumonia – Grade 3, Unrelated	0	1 (0.6%)
Pneumonia – Grade 5, Unrelated	1 (0.6%)	0
Injury, poisoning and procedural complications	**0**	**1 (0.6%)**
Femoral neck fracture – Grade 3, Unrelated	0	1 (0.6%)
Metabolism and nutrition disorders	**1 (0.6%)**	**1 (0.6%)**
Diabetes mellitus inadequate control – Grade 2, Unrelated	0	1 (0.6%)
Hyponatraemia – Grade 2, Unrelated	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	**1 (0.6%)**	**0**
Vertebral end plate inflammation – Grade 3, Unrelated	1 (0.6%)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2 (1.1%)**	**0**
Clear cell renal cell carcinoma – Grade 3, Unrelated	1 (0.6%)	0
Hepatocellular carcinoma – Grade 3, Unrelated	1 (0.6%)	0
Renal cancer – Grade 3, Unrelated	1 (0.6%)	0
Nervous system disorders	**1 (0.6%)**	**2 (1.1%)**
Carotid artery stenosis – Grade 3, Unrelated	1 (0.6%)	0
Cerebral infarction – Grade 3, Unrelated	0	1 (0.6%)
Ischaemic stroke – Grade 3, Related	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**2 (1.1%)**	**0**
Dyspnoea – Grade 5, Unrelated	1 (0.6%)	0
Pulmonary embolism – Grade 4, Unrelated	1 (0.6%)	0
Skin and subcutaneous tissue disorders	**3 (1.7%)**	**3 (1.7%)**
Decubitus ulcer – Grade 3, Unrelated	0	1 (0.6%)
Diabetic foot – Grade 2, Unrelated	1 (0.6%)	0

Diabetic foot – Grade 3, Unrelated	1 (0.6%)	1 (0.6%)
Diabetic ulcer – Grade 3, Unrelated	0	2 (1.1%)
Skin ulcer – Grade 3, Unrelated	1 (0.6%)	0
Vascular disorders	**1 (0.6%)**	**2 (1.1%)**
Arteriosclerosis – Grade 3, Unrelated	0	1 (0.6%)
Dry gangrene – Grade 3, Unrelated	1 (0.6%)	0
Peripheral artery occlusion – Grade 3, Unrelated	0	1 (0.6%)
Vascular occlusion – Grade 3, Unrelated	0	1 (0.6%)

Note: The total number of TESAEs counted includes events for all patients in the Safety Set for Main Study Period. At each level of summarization, patients are counted once if they reported one or more events.

2.5.8.4. Laboratory findings

Clinical Laboratory Evaluations

For all clinical chemistry and haematology laboratory parameters, there were very few patients who had shifts from normal at baseline to abnormal at a postbaseline visit during the overall study period. There were no notable differences between the CT-P42 group and the EU-approved Eylea group in shifts from baseline in clinical chemistry and haematology laboratory parameters.

In Main Study Period, the majority of laboratory parameters CTCAE grade 2 or lower for each laboratory parameter. The most frequently reported grade 3 laboratory parameter was hyperkalaemia (5 [2.9%] and 6 [3.4%] patients in CT-P42 and EU-approved Eylea groups, respectively). Grade 4 laboratory parameters reported were creatinine increased (1 [0.6%] patient in the CT-P42 group), hypertriglyceridemia (1 [0.6%] patient in the EU-approved Eylea group) and hyperkalaemia (1 [0.6%] patient in each treatment group). None of grade 5 laboratory parameters were reported in any treatment group. In Extension Study Period, no notable trends were observed following one dose of CT-P42.

Any abnormality of the test result was reported as a TEAE if it was determined to be clinically significant by the investigator.

Vital Signs and Weight

In Main Study Period, there were no notable trends in changes from baseline or notable differences between treatment groups in any of the vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature). During Extension Study Period, no notable trends were observed following one dose of CT-P42.

Hypersensitivity Monitoring

In Main Study Period, the most commonly reported clinically notable vital sign results during hypersensitivity monitoring were high respiratory rate and high diastolic blood pressure. However, in general, there were no differences between the treatment groups in the proportions of patients with high respiratory rate and high diastolic blood pressure. No other clinically notable vital sign parameter results during hypersensitivity monitoring were reported. During Extension Study Period, no notable trends were observed following one dose of CT-P42.

Electrocardiogram

In Main Study Period, the majority of patients had normal or non-clinically significant abnormal baseline electrocardiogram (ECG) results except 1 patient in the CT-P42 group who reported ongoing medical history of bundle branch block left. During Main Study Period, one patient in the CT-P42 group reported new clinically significant abnormal ECG results of non-specific changes in anterolateral repolarization which was possible coronary ischemia and NYHA Class III at EOS1 visit. Based on these findings, the patient reported a TEAE of myocardial infarction. One patient in the EU-approved Eylea group reported new clinically significant abnormal ECG results and this was reported as TEAE of leading to discontinuation (cardiac failure). During Extension Study Period, no clinically significant abnormal ECG results were reported.

New York Heart Association Functional Classification

The majority of patient did not have heart failure, and no other clinically significant abnormalities related to the study drug were reported at Screening and Week 0. Three patients reported NYHA Class III at EOS1 visit and no patients reported NYHA Class IV during Main Study Period. One patient in the Eylea group reported worsening of heart failure with NYHA Class III at the unscheduled visit after Week 4 and reported a TEAE of cardiac failure, resulting in the early study termination due to this event. One patient in the CT-P42 group reported new clinically significant abnormal ECG results of non-specific changes in anterolateral repolarization which was possible coronary ischemia and NYHA Class III at EOS1 visit. Based on these findings, the patient reported a TEAE of myocardial infarction. One patient in the CT-P42 group reported NYHA Class III at EOS1 visit related to coronary artery disease 43 days after Week 24 visit and discontinued from the study due to this event.

Physical Examination

The majority of patients had normal baseline physical examination results, and no one reported clinically significant abnormalities at post-treatment visits except 2 patients. One patient in the EU-approved Eylea group reported a new clinically significant abnormal result for the respiratory system at unscheduled visit after Week 4 due to a TEAE of cough. One patient in the CT-P42 group reported a new clinically significant abnormal result for the cardiovascular system at EOS1 visit due to TESAE of coronary artery disease. During Extension Study Period, no clinically significant abnormal results were reported.

Finger Count, Hand Motion, and Light Perception

After each IVT injection, the majority of patients did not have difficulties in finger count except 3 patients in the CT-P42 group. Three patients failed in finger count once but they were able to see hand motion. Therefore, no related TEAEs were reported in Main Study Period. During Extension Study Period, all patients did not have difficulties in finger count.

Intraocular Pressure Measurements

Mean IOP in the study eye were similar between CT-P42 and EU-approved Eylea groups. From baseline through overall study period, the mean IOP in the study eye fluctuated between 15.2 mmHg and 18.3 mmHg in the CT-P42 group and between 15.5 mmHg and 18.1 mmHg in the EU-approved Eylea group. During Extension Study Period, no notable trends were observed following one dose of CT-P42.

In addition, post hoc analysis for proportions of patients with IOP ≥ 30 mmHg was conducted. The proportion of patients with at least one IOP ≥ 30 mmHg after the study drug administration in the study eye was similar between the treatment groups (1 [0.6%] and 5 [2.9%] patients in the CT-P42 and EU-approved Eylea groups, respectively).

Slit Lamp Examination

During Main Study Period, there were no notable differences in slit lamp examination results in the study eye between CT-P42 and EU-approved Eylea groups. During Extension Study Period, no new clinically significant findings were observed in the study eye.

Indirect Ophthalmoscopy

During Main Study Period, the results of pre-injection and post-injection indirect ophthalmoscopy were generally similar between CT-P42 and EU-approved Eylea groups. All clinically relevant findings during the study were to be reported as ocular AEs. During Extension Study Period, no new clinically significant findings were observed in the study eye.

Safety in Special Groups and Situations

In Study CT-P42 3.1, incidences of patients reporting TEAEs were also compared using the subgroups for age (<65, ≥65 years), race (Asian, White) and sex (male, female) to assess whether these were factors influencing safety of CT-P42 relative to EU-approved Eylea.

The overall safety profile of CT-P42 in DME patients was generally similar to that of EU-approved Eylea in the age, race and sex subgroups. The results of these subgroup analyses did not reveal specific safety concerns for CT-P42 in relation to specific age, race and sex subgroups.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not available

2.5.8.6. Safety in special populations

Not applicable

2.5.8.7. Immunological events

The applicant has adopted an electrochemiluminescence immunoassay (ECLIA) bridging assay to screen, confirm and quantify aflibercept specific antibodies in human serum matrix. The adopted three-tiered approach for determination of ADAs was well described and developed and considered state of the art.

Further, the applicant presented a qualitative assay for the detection of neutralising ADA's in human serum. The presented assay was well described and established.

Out of 7 patients in total (3 and 4 patients in the CT-P42 and Eylea groups, respectively) reported as at least one ADA positive after study drug administration, 4 patients (2 patients in each of the treatment groups) experienced at least 1 treatment-emergent adverse event (TEAE) and there was no study drug related TEAE. In addition, there were no patients who experienced treatment-emergent serious adverse event (TESAE) or TEAE leading to study drug discontinuation. As the number of ADA positive patients was very limited, the impact of immunogenicity on safety could not be assessed.

Please see Section 2.5.2.2 and 2.5.3 in this report for further evaluation of immunological events.

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

Not applicable

2.5.8.9. Discontinuation due to adverse events

In each treatment group, 6 (3.4%) patients experienced at least 1 TEAE leading to study drug discontinuation in Main Study Period. Among them, all of the TEAEs leading to study drug discontinuation were non-ocular TEAEs except 2 cases of ocular TEAEs in the study eye (one case in each treatment group). The TEAEs leading to study drug discontinuation considered to be related to the study drug were reported for 1 (0.6%) patient (macular ischaemia, grade 3) in the CT-P42 group and 1 (0.6%) patient (ischaemic stroke, grade 3) in the Eylea group.

No patient experienced a TEAE leading to study drug discontinuation in Extension Study Period.

2.5.8.10. Post marketing experience

Not available

2.5.9. Discussion on clinical safety

The safety assessment of the aflibercept biosimilar candidate CT-P42 was conducted by taking into account the known safety profile of the reference product Eylea. This is line with the overall concept of comparable safety evaluation for a similar biological medicinal product.

The clinical safety assessment of CT-P42 is based on one phase 3 study (Study CT-P42 3.1), a randomized, active-controlled, double-masked, parallel-group and multicentre study to compare efficacy and safety of CT-P42 in comparison with Eylea in patients with DME.

The total safety database for CT-P42 in this application consists of 348 patients with DME (174 in each treatment group) who were exposed to CT-P42 or EU-approved Eylea at a dose of 2 mg per IVT injection every 4 weeks for 5 doses, and then every 8 weeks for 4 doses in the Main Study Period. After that, 31 patients (15 and 16 patients from the CT-P42 and EU-approved Eylea groups, respectively) entered the Extension Study Period where they received 1 additional dose of CT-P42 and were observed for an additional 4 weeks. The number of total doses received was comparable between treatments (mean (SD) of 8.5 (1.4) and 8.4 (1.6) in the test and reference group, respectively).

In the Main Study Period, one patient who was randomly assigned to the EU-approved Eylea group, was administered CT-P42 at the Week 40 visit due to a dispensation error. Patients were analysed based on the treatment actually that they received. In the Extension Study Period, 30 patients received one dose of CT-P42 PFS and 1 patient wrongly received CT-P42 vial at Extension Week 0. All of them were included in the Safety Set for Extension Study Period in accordance with the definition of the analysis set.

The safety profile of Eylea is well-established and the safety database of 174 patients treated for up to 52 weeks with CT-P42 was considered sufficient for the general evaluation of safety and immunogenicity of CT-P42 in comparison to the reference product.

The overall number [proportion] of patients who experienced at least 1 TEAE in Study CT-P42 3.1 was 109 [62.6%] and 117 [67.2%] patients in the CT-P42 and Eylea groups, respectively, and the total number of TEAEs was 269 and 318, respectively.

The proportion of patients with at least 1 overall TEAE, as well as of those with TEAE related to injection procedure (4.0% and 9.2%), TEAE in the study eye (17.8% and 21.8%), TEAE in the fellow eye (21.3% and 25.9%) and non-ocular TEAE (49.4% and 53.4%) was lower in the CT-P42 group compared to the Eylea group. The incidences of TEAE related to study-drug, TESAE, TEAE leading to discontinuation of study drug and TEAE leading to death were overall comparable between treatments.

The number [proportion] of patients who experienced at least 1 ocular TEAE in the study eye was 31 [17.8%] and 38 [21.8%] patients in the CT-P42 and Eylea groups, respectively. The total number of ocular TEAEs in the study eye was 109 (CT-P42: 48; Eylea: 61). The most frequently reported ocular TEAE by PT in the study eye was intraocular pressure increased (3 [1.7%] and 4 [2.3%] patients, respectively), followed by conjunctival haemorrhage (2 [1.1%] and 4 [2.3%] patients, respectively).

The number [proportion] of patients who experienced at least 1 ocular TEAE in the fellow eye was 37 [21.3%] and 45 [25.9%] patients in the CT-P42 and Eylea groups, respectively. A total of 102 ocular TEAEs in the fellow eye were reported (CT-P42: 47; Eylea: 55). The most frequently reported ocular TEAE by PT in the fellow eye was diabetic retinal oedema (17 [9.8%] and 23 [13.2%] patients, respectively), followed by cataract (3 [1.7%] and 2 [1.1%] patients, respectively), epiretinal membrane (3 [1.7%] and 2 [1.1%] patients, respectively), and visual acuity reduced (4 [2.3%] and 1 [0.6%] patients, respectively). No TESAE was reported in the fellow eye and all the TEAEs in fellow eye were considered unrelated to the study drug.

The number [proportion] of patients who experienced at least 1 non-ocular TEAE was 86 [49.4%] and 93 [53.4%] patients in the CT-P42 and EU-approved Eylea groups, respectively. The most frequently reported non-ocular TEAE by PT was hypertension (11 [6.3%] and 16 [9.2%] patients, respectively), followed by COVID-19 (8 [4.6%] and 10 [5.7%] patients, respectively).

Overall, the majority of patients experienced TEAEs that were not related to study drug (CT-P42: 61.5%; Eylea: 66.1%). The proportion of patients who had at least 1 TEAE considered by investigator to be related to the study drug was slightly higher in the CT-P42 group compared to the Eylea group (4.6% and 3.4%, respectively) in the Main Study Period. Study drug related ocular TEAEs in the study eye were reported for 4.0% and 2.3% patients in the CT-P42 and Eylea groups, respectively. Except for intraocular pressure increased (CT-P42: 1.1%; Eylea: 1.7%), which was the most frequently reported study drug related ocular TEAE in the study eye, all of these events were reported only in one patient. None of the ocular TEAEs in the fellow eye were considered by investigator to be related to the study drug. Study drug related non-ocular TEAEs were reported slightly less frequently in the CT-P42 group than the Eylea group (0.6% and 1.7%, respectively).

Most patients experienced TEAEs with grade 1 or 2 in intensity. In the Main Study Period, the number (%) of patients who experienced at least 1 common terminology criteria for AE (CTCAE) grade 3 or higher TEAE was 40 (23.0%) and 41 (23.6%) patients in the CT-P42 and EU-approved Eylea groups, respectively. The most frequently reported grade 3 or higher TEAE by SOC was eye disorders (10 [5.7%] and 5 [2.9%] patients, respectively) and by PT was hypertension (2 [1.1%] and 4 [2.3%] patients, respectively).

The number (%) of patients who experienced at least one CTCAE grade 3 or higher ocular TEAE in the study eye was 5 (2.9%) and 3 (1.7%) patients in the CT-P42 and EU-approved Eylea groups, respectively. All these events were grade 3 in intensity. The reported grade 3 ocular TEAEs in the study eye were cataract, epiretinal membrane, macular ischaemia, visual impairment, eye contusion, and intraocular pressure increased (1 [0.6%]

patient each) in the CT-P42 group and retinal vein occlusion, ulcerative keratitis (1 [0.6%] patient each) and visual acuity reduced (2 [1.1%] patients) in the Eylea group.

The proportion of patients who experienced at least 1 CTCAE grade 3 or higher non-ocular TEAE in the study eye was similar in both groups (18.4% and 20.7%, respectively). Most of these were grade 3, with only 1.1% of the patients experiencing grade 4 non-ocular TEAEs and 1.7% (CT-P42) and 1.1% (Eylea) experiencing grade 5 non-ocular TEAEs.

During the Extension Period, only 3 (9.7%) patients who received CT-P42 experienced at least 1 TEAE, all of which were Grade 1 or Grade 2 in intensity. All of those TEAEs were reported as non-ocular TEAEs except 1 ocular TEAE in the fellow eye. All TEAEs were considered to be unrelated to the study drug.

The observed imbalances in certain categories of adverse events during the Main Study Period are not apparently related to any imbalances in the study population, as demographic characteristics as well as ocular and non-ocular medical and surgical history, were balanced across treatment arms. Further, the proportions of patients taking concomitant medication of various classes were generally similar between the treatment groups.

Overall, the observed imbalances in certain categories of adverse events during the Main Study Period were mostly within 5% between groups and are not considered clinically relevant.

A total of 5 patients died due to TEAEs during the study (3 [1.7%] and 2 [1.1%] patients in the CT-P42 and EU-approved Eylea group, respectively). The narratives for all affected patients have been provided by the applicant. None of the events leading to death were considered related to the study drug or injection procedure. All patients had prior/concomitant comorbidities and the events of death were attributed to concomitant disease in most cases.

The proportion of patients who experienced at least 1 TESAE was similar between the treatment groups in the Main Study Period (19 [10.9%] and 17 [9.8%] patients in the CT-P42 and Eylea groups, respectively). The most frequently reported non-ocular TESAEs by PT were cardiac failure (1 [0.6%] and 2 [1.1%] patients, respectively) and diabetic foot (2 [1.1%] and 1 [0.6%] patients, respectively).

All TESAEs were non-ocular TESAEs and most of the events were considered unrelated to the study drug. Only 1 grade 3 TESAE of myocardial infarction reported in the CT-P42 group and 1 grade 3 TESAE of ischaemic stroke reported in the Eylea group were considered to be related to the study drug. The event in the CT-P42 group occurred 4 days after the Week 8 dose administration and resolved after both medication and non-medication treatment. The event in the Eylea group occurred 47 days after the Week 24 dose administration and resolved with sequelae (subject apathetic, weakened, with mobility difficulties) after medications treatments. In both cases, the investigator confirmed that the patient's medical history was assessed as a possible risk factor for the event.

According to the Eylea SmPC, there is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the Eylea clinical trials in patients with AMD, DME, RVO, myopic CNV and ROP. Thus, the observed events in Study CT-P42 3.1 are not considered unexpected serious adverse reactions.

All other TESAEs were considered to be unrelated to the study drug.

Most patients experienced TESAEs with grade 2 or 3 in intensity. In the Main Study Period, the number (%) of patients who experienced at least 1 grade 4 or higher TESAE was 4 (2.3%) patients in the CT-P42 and Eylea groups each.

No TESAE or TEAE leading to study drug discontinuation occurred during the Extension Study Period.

Arterial thromboembolic events (ATEs) and TEAEs related to IVT injection procedure were considered AESIs by considering Eylea's safety profile and were closely monitored.

The incidence of ATE was comparable between treatment groups in the Main Study Period, (8 (4.6%) patients per group experienced at least 1 ATE). The most frequently reported TEAE classified as ATE was carotid artery stenosis (1 [0.6%] and 2 [1.1%] patients in the CT-P42 and Eylea groups, respectively). All of the ATEs were non-ocular TEAEs and considered to be unrelated to the study drug except for the two cases described under TESAEs.

The proportion of patients who experienced at least 1 ocular TEAE related to IVT injection procedure in the study eye was lower in the CT-P42 group (7 [4.0%] patients) compared to the Eylea group (15 [8.6%] patients). Most of the events were unrelated with the study drug and the proportion of patients who experienced study drug related ocular events in the study eye was similar between the treatment groups (2 [1.1%] and 3 [1.7%] patients, respectively).

The most frequently reported ocular TEAEs related to IVT injection procedure in the study eye were conjunctival haemorrhage and intraocular pressure increased (1 [0.6%] and 4 [2.3%] patients in the CT-P42 and Eylea groups, respectively for both term).

Ocular TEAEs related to IVT injection procedure in the fellow eye were only reported in the Eylea group. However, the incidence rate was low (3 events reported in 2 (1.1%) patients), and all events were considered to be unrelated to the study drug. Additionally, 1 non-ocular TEAE of hypertension (grade 3) related to IVT injection procedure was reported in 1 (0.6%) patient in the Eylea group and this case was also considered to be unrelated to the study drug.

No TEAE related to IVT injection procedure occurred in the Extension Study Period.

TEAE leading to study drug discontinuation were experienced by 6 patients per group. Of those, only one patient per group experienced an ocular TEAE leading to discontinuation. Most of the events were not considered to be related to study drug, except for one case per group. Those cases were 1 (0.6%) patient with macular ischaemia, grade 3, in the CT-P42 group and 1 (0.6%) patient with ischaemic stroke, grade 3, in the Eylea group. Macular ischaemia is not specifically pointed out as an adverse drug reaction in the SmPC of the reference product and the applicant was required to provide further discussion in relation to this TEAE with the responses to the D120 LoQ. This TEAE of macular ischaemia reported in the CT-P42 treatment group occurred in the study eye of a 68-year-old male patient at the Week 24 visit (58 days after study drug injection at Week 16). The event was further described as macular arterial ischaemia by the investigator. The patient's medical history included type 2 diabetes mellitus, hypertension, and diabetic retinopathy (DR) in both eyes. Specifically, the DR condition, though initially not so severe as to lead to an exclusion from the study, worsened throughout the time the patient spent on the trial from moderate non-proliferative DR to mild proliferative DR. Additional post-hoc image review of the Fundus Photography and Fluorescein Angiography images from the EOS visit indicated advanced diabetic retinopathy with occlusion of retina artery branches in the ischaemic area. Thus, it was suggested that the vascular occlusion was a consequence of the microvascular changes due to diabetic retinopathy. Therefore, although the event had been judged as possibly drug-related by the investigator, there is a strong probability that it was a sequalae of the patient's underlying medical condition.

Further, the applicant provided literature related to a possible risk of macular ischaemia by anti-VEGF treatment in general. Already in 2012, Manousaridis and Talks concluded that, "anti-VEGF therapy rarely seems to further compromise the retinal circulation; however, worsening of macular ischaemia in the long term cannot be

definitely excluded, particularly in eyes with significant ischaemia at baseline and after repeated intraocular anti-VEGF injections." In another study, progressive macular ischaemia was reported in one patient treated for diabetic macular oedema by combination therapy of aflibercept and targeted retinal laser photocoagulation (Cornish, 2023). It has thus been shown that sporadic cases of macular ischaemia may occur in patients treated with aflibercept, although this is not reflected in the originator SmPC.

Overall, it can be concluded that the single case of macular ischaemia does not significantly impact the safety profile of CT-P42 in comparison to Eylea.

In the Extension Study Period a single dose was administered; study drug discontinuation was therefore not applicable. In addition, none of the patients included in the Extension Study Period discontinued early from the study.

The incidence of TEAE related to clinical chemistry and haematology laboratory parameters was overall low and comparable between groups. Any abnormalities of test results were reported as a TEAE if determined to be clinically significant by the investigator. The same holds true for vital signs and related parameters. During the Extension Study Period, no clinically significant abnormal results were reported in any of the laboratory, physical or other examinations related to safety.

Mean intraocular pressure (IOP) measurements in the study eye were similar between the CT-P42 and EU-approved Eylea groups. From baseline through overall study period, the mean IOP in the study eye fluctuated between 15.2 mmHg and 18.3 mmHg in the CT-P42 group and between 15.5 mmHg and 18.1 mmHg in the EU-approved Eylea group. Proportions of patients with IOP ≥ 30 mmHg were compared via post hoc analysis. The proportion of patients with at least one IOP ≥ 30 mmHg after study drug administration in the study eye was similar between the treatment groups.

Also, the results of results of pre-injection and post-injection indirect ophthalmoscopy as well as of slit lamp examination were generally similar between CT-P42 and EU-approved Eylea groups. All clinically relevant findings during the study were reported as ocular TEAEs.

Incidences of patients reporting TEAEs were also compared using the subgroups for age (<65, ≥65 years), race (Asian, White) and sex (male, female) to assess whether these were factors influencing safety of CT-P42 relative to EU-approved Eylea. The overall safety profile of CT-P42 in DME patients was generally similar to that of EU-approved Eylea in the age, race and sex subgroups and the results did not reveal specific safety concerns for CT-P42 in relation to specific age, race and sex.

Usability

Safety results from Extension Study Period showed no notable safety concerns following CT-P42 PFS administration. However, the sample size of the extension period was not sufficient to allow for a proper safety assessment.

Immunogenicity

Immunological events are discussed in the section on clinical pharmacology.

2.5.10. Conclusions on the clinical safety

The overall safety profile of CT-P42 appears comparable to the safety profile of the reference product Eylea as it is stated in the product information.

2.6. Risk Management Plan

2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 33: 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-foetotoxicity
Missing information	None

Note: The missing information 'Long-term safety of aflibercept in preterm infants with retinopathy of prematurity', is not included in this table because Eydenzelt is not indicated in preterm infants for the treatment of Retinopathy of Prematurity.

2.6.2. Pharmacovigilance plan

There are no on-going or planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan for Aflibercept (M710 or MYL-1701P).

No additional pharmacovigilance activities are proposed by the MAH. Based on the current information, this is endorsed.

2.6.3. Risk minimisation measures

Table 34: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Endophthalmitis (likely infectious origin)	**Routine risk communication:** SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:**

	• Treatment with Eydenzelt is contraindicated in patients with Ocular or periocular infection and active severe intraocular inflammation (SmPC Section 4.3). • Recommendation for administering the drug, and monitoring and reporting any symptoms suggestive of endophthalmitis following the IVT injection of Eydenzelt is given in SmPC Section 4.2 and 4.4. • Guidance is given in PL Section 2 for patients to recognise early signs and symptoms of infection and how to manage this risk. • Information is given in PL Section 3 for patients about how the doctor will disinfect the eye before injection to prevent infection. **Other routine risk minimization measures beyond the Product Information:** *Legal status:* Medicinal product subject to restricted medical prescription. *Eydenzelt* must only be administered by a qualified physician experienced in administering intravitreal injections.
Intraocular inflammation	**Routine risk communication:** SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Treatment with Eydenzelt is contraindicated in patients with active severe intraocular inflammation (SmPC Section 4.3). • Recommendation for administering the drug, and monitoring and reporting any symptoms of intraocular inflammation, is given in SmPC Section 4.2 and 4.4. • Guidance is given in PL Section 2 for patients to recognise early signs and symptoms of infection or inflammation and how to manage this risk. Information is given in PL Section 3 for patients about how the doctor will disinfect the eye before injection to prevent infection. **Other routine risk minimization measures beyond the Product Information:** *Legal status:* Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Transient intraocular pressure increase	**Routine risk communication:** SmPC sections 4.2, 4.4, 4.8 and 4.9 PL sections 2 and 4

	Routine risk minimization activities recommending specific clinical measures to address the risk: •Recommendation for physicians for administering the drug, and monitoring and management of intraocular pressure, immediately following IVT injection is given in SmPC Section 4.2 and 4.4. • Information is given in SmPC Section 4.2, that the excess volume must be expelled before injecting the recommending dose. • Advice in provided in SmPC Section 4.9 about monitoring and management of intraocular pressure increase caused by overdose. • Information is given in PL Section 2 for patients regarding the increase in eye pressure within 60 minutes of Eydenzelt injection and that the doctor will monitor the eye pressure after each injection. **Other routine risk minimization measures beyond the Product Information:** *Legal status:* Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Retinal pigment epithelial tears	**Routine risk communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Guidance for physicians regarding the caution to be used in patients with risk factors for retinal pigment epithelial tears is mentioned in SmPC Section 4.4. • Guidance is given in PL Section 2 for patients regarding the risk factors for retinal pigment epithelial tears and the caution to be followed while giving Eydenzelt in such cases. **Other routine risk minimization measures beyond the Product Information:** *Legal status:* Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Cataract (especially of traumatic origin)	**Routine risk communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4

	Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for physicians for administering the drug is given in SmPC Section 4.2. Special precaution to physicians for using proper aseptic injection techniques when administering Eydenzelt and monitoring for symptoms during the week following the injection are provided in SmPC Section 4.4. • Advice to instruct adult patients to report any symptoms suggestive of traumatic cataract without delay is mentioned in SmPC Section 4.4. • Guidance is given in PL Section 2 for patients to recognise and report immediately, the symptoms of inflammation inside the eye. • Information is given in PL Section 3 for patients about how the doctor will disinfect the eye to prevent infection. **Other routine risk minimization measures beyond the Product Information:** *Legal status:* Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Medication errors	**Routine risk communication:** SmPC sections 4.2, 4.9 and 6.6 PL sections 1 and 3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation is provided in the SmPC Section 4.2 regarding the correct method of administration of Eydenzelt to minimise the risk of drug administration error. • Advice in provided in SmPC Section 4.9 about monitoring and management of overdose. • Detailed and illustrated instructions for the use of the PFS is provided in SmPC Section 6.6 and PL Section 'information intended for HCPs only', in order to minimise the risk of drug administration error. **Other routine risk minimization measures beyond the Product Information:** *Legal status:* Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Off-label use and misuse	**Routine risk communication:** SmPC sections 4.1, 4.3, 4.4 and 4.6

	PL sections 1, 2, and 3 **<u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u>** • Recommendation on conditions in which treatment is contraindicated or should be withheld/discontinued are provided in SmPC Sections 4.3 and 4.4. • Recommendation for use in pregnancy and breastfeeding is given in SmPC Section 4.6. • Contraindications, conditions in which treatment should be withheld/discontinued, and recommendation on use during pregnancy/breastfeeding are mentioned in PL Section 2. **<u>Other routine risk minimization measures beyond the Product Information:</u>** *Legal status:* Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.
Embryo-fetotoxicity	**<u>Routine risk communication:</u>** SmPC sections 4.4, 4.6 and 5.3 PL section 2 **<u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u>** • Recommendation and advice is given in SmPC Section 4.4 and 4.6 regarding the use during pregnancy and breastfeeding, and regarding the use of effective contraception during treatment. • Advice is given in PL Section 2 for patients regarding the use during pregnancy and breastfeeding, and use of effective contraception during treatment. • Advice is given in PL Section 2 for patients to inform the doctor if the patient is pregnant or planning to get pregnant before using Eydenzelt. **<u>Other routine risk minimization measures beyond the Product Information:</u>** *Legal status:* Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.

Additional Risk Minimisation Measures

Besides the routine risk minimisation activities (SmPC and patient information), additional activity, specifically an educational programme is considered to be necessary for the important identified risks of endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment

epithelium tears, cataract (especially of traumatic origin), as well as for the important potential risk of medication errors, off-label use and misuse, embryo-fetotoxicity. Generally, the educational material covers the indications wet AMD, CRVO, BRVO, myopic CNV and DME.

The applicant proposed a prescriber guide and a patient guide to educate HCPs, patients/caregivers about specific risks, their early symptoms and the best course of action to be taken when these appear beyond the recommendations contained in the Product Information. The details are available in Annex 6 "Details of Proposed Additional Risk Minimisation Activities" and contain a physician information, intravitreal injection procedure pictogram, intravitreal injection procedure video, and a patient information pack which includes a patient information guide and its audio version.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	Routine risk minimisation measures: SmPC Sections 4.3 and 4.8. SmPC Sections 4.2 and 4.4 where recommendations for administering the drug, monitoring and reporting any symptoms suggestive of endophthalmitis following the IVT injection of Eydenzelt are included. PL Sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Target follow-up questionnaire Additional pharmacovigilance activities: None
Intraocular inflammation	Routine risk minimisation measures: SmPC Sections 4.3 and 4.8. SmPC Sections 4.2 and 4.4 where recommendations for monitoring and	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Target follow-up questionnaire

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	reporting any symptoms of intraocular inflammation are included. PL Sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Additional pharmacovigilance activities: None
Transient intraocular pressure increase	Routine risk minimisation measures: SmPC Sections 4.8 and 4.9. SmPC Section 4.2 and 4.4 where guidance for physicians for monitoring and management of intraocular pressure, immediately following IVT injection are included. PL Sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Target follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	
Retinal pigment epithelial tears	Routine risk minimisation measures: SmPC Section 4.8. SmPC Section 4.4 where caution to be used in patients with risk factors for retinal pigment epithelial tears is mentioned. PL Sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Cataract (especially of traumatic origin)	Routine risk minimisation measures: SmPC Sections 4.2, 4.8. SmPC Section 4.4 where advice to physicians for using proper aseptic injection techniques when administering Eydenzelt and monitoring for symptoms during the week following the injection is provided. Additionally, the Section 4.4 advises to instruct adult patients to report any symptoms suggestive of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	traumatic cataract without delay. PL Sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	
Medication errors	Routine risk minimisation measures: SmPC Section 4.9. SmPC Section 4.2 where the correct method of administration of Eydenzelt is provided in detail to minimise risk of drug administration error. Section 4.9 provides information on monitoring and management of overdose. SmPC Section 6.6 where detailed and illustrated instructions are provided for the use of the PFS. PL Sections 1 and 3 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	
Off-label use and misuse	Routine risk minimisation measures: SmPC Sections 4.1, 4.6. SmPC Sections 4.3 and 4.4 where recommendation on conditions in which treatment is contraindicated or should be withheld/discontinued are provided. PL Sections 1, 2 and Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Embryo-fetotoxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3. SmPC Section 4.4 which advises that Eydenzelt should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	

2.6.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. 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.

2.8. Non-conformity of paediatric studies

Not applicable.

2.9. Product information

2.9.1. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Eydenzelt (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

Eydenzelt (CT-P42, INN: aflibercept) has been developed as a biosimilar to the reference product Eylea.

The reference product Eylea is authorised in 3 presentations: Eylea 40 mg/mL solution for injection in pre-filled syringe, Eylea 40 mg/mL solution for injection in a vial and Eylea 114.3 mg/ml solution for injection. The approved indications differ for respective presentations as follows:

- Eylea 40 mg/mL solution for injection in pre-filled syringe: nAMD, branch RVO or central RVO, DME, myopic CNV in adults. This presentation has an additional indication in preterm infants which is not authorised for other presentation: for the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.
- Eylea 40 mg/mL solution for injection in a vial: nAMD, branch RVO or central RVO, DME, myopic CNV in adults
- Eylea 114.3 mg/ml solution for injection: nAMD and DME in adults

CT-P42 vial and PFS is formulated as a solution for intravitreal injection at the same strength (40 mg/mL) to the reference product Eylea. Each presentation provides a volume to enable delivery of a single dose of 50 µL containing 2 mg aflibercept.

CELLTRION applied to obtain approval for all indications that are currently approved for EU-approved Eylea except for retinopathy of prematurity (ROP).

Quality

The applicant performed a comprehensive analytical biosimilarity exercise comparing CT-P42 (using DP lots from clinical and commercial process versions) and the reference medicinal product EU-approved Eylea. A sufficient number of CT-P42 and EU-approved Eylea lots including both presentations (vial/PFS), which can be

expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product, was included. Comparability of CT-P42 manufactured according to the different process versions as well as of both presentations of CT-P42 has been demonstrated. In addition to the main similarity study, additional extensive comparative studies focussing on characterisation of the charge variants, the impact of glycosylation, and further comparison of VEGF receptor domain related functional activities were performed. Furthermore, comparative forced degradation studies have been performed.

The relevant quality attributes of the aflibercept molecule were assessed using a broad panel of orthogonal standard and state-of-the art techniques. Physicochemical analyses covered primary sequence and higher order structure, glycosylation and other post-translational modifications, size and charge variants, 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 that is mediated by the VEGF receptor domain and Fc domain-related functions. Based on the provided information it is concluded that the analytical methods are suitable and sensitive to detect minor differences.

For the main similarity study, functional attributes related to the MoA, FcRn binding, and protein content were evaluated against a quality range. Physicochemical attributes and functional activities not related to the MoA were compared in a descriptive way under consideration of mean and data spread without applying statistical comparability ranges. A rather general justification is provided for the chosen statistical approach; the underlying similarity condition, operational characteristics of the selected similarity criterion etc are not discussed by the applicant. However, analytical results including chromatograms, spectra, response curves etc. for the individual lots have been provided and enable an independent assessment. Results of the additional comparative studies were also compared in a descriptive way.

Clinical

The clinical development program to support the similarity of CT-P42 to Eylea comprises one Phase 3 therapeutic similarity study (Study CT-P42 3.1), "A Phase 3, double-masked, randomized, active-controlled, parallel group study to compare efficacy and safety of CT-P42 and EU-approved Eylea in patients with DME".

The primary objective of this study was to demonstrate the equivalence in efficacy of CT-P42 compared to Eylea in subjects with diabetic macular oedema (DME) with the primary efficacy endpoint "change from baseline in BCVA using the ETDRS chart at Week 8".

A separate clinical Phase 1 PK study was not conducted, since it was considered not meaningful to determine the biosimilarity based on the low level of aflibercept in serum following IVT administration. Maximum concentration (C_{max}) and time to maximum concentration (T_{max}) of free (VEGF-unbound) study drug concentrations in plasma were assessed as secondary PK endpoints in Study CT-P42 3.1, at pre-dose as well as 24 hours, 48 hours and 72 hours after both the 1st and the 5th study drug administration.

3.2. Results supporting biosimilarity

Quality

For many quality attributes including those related to the MoA analytical similarity between CT-P42 and the reference product EU-approved Eylea was demonstrated. The observed minor analytical differences have been adequately evaluated and justified regarding their impact on clinical performance of the product.

A detailed characterisation of charge variants revealed the presence of the same variants for both CT-P42 and EU-approved Eylea. Additional studies investigating the impact of glycosylation on biological activities show comparable results for both products.

Similar degradation profiles and kinetics were determined for CT-P42 and the reference product under thermal, oxidative, UV light, and low/high pH stress further supporting biosimilarity.

Clinical

Pharmacokinetics

The observed systemic aflibercept concentrations in patients' plasma were generally low (mean Cmax approximately 42 to 68 ng/mL) and comparable with known data for the reference product (mean Cmax values of free aflibercept in plasma in the range of 30 to 50 ng/mL).

The observed low plasma concentrations of free drug attest that there is no relevant systemic exposure.

Efficacy

In Study CT-P42 3.1, the primary endpoint "change from baseline in BCVA using the ETDRS chart at Week 8" was considered to be a sensitive endpoint to detect differences between the biosimilar candidate and the reference product and thus appropriate for this comparative clinical evaluation. Equivalence between the main treatment groups was to be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters], which was considered an appropriate margin, since ± 3 letters reflect low or no clinical relevance.

In the FAS, the observed LS mean change for BCVA at week 8 was similar between the CT-P42 and Eylea groups (9.43 letters and 8.85 letters respectively). The 95% CI of (-0.73, 1.88) for the treatment difference in BCVA at week 8 was entirely within the pre-defined equivalence margin of ±3 letters.

In the PP set the observed LS mean change for BCVA at week 8 was similar between the CT-P42 and Eylea groups (9.22 letters and 8.84 letters respectively). The 95% CI of (-0.90, 1.66) for the treatment difference was entirely within the equivalence margin of ±3 letters.

A sensitivity analysis was performed to assess the impact of missing data on the primary analysis by using multiple imputation with the missing at random assumption in the FAS. The results from the sensitivity analysis were similar to the results from the primary analysis using the FAS (treatment difference of 0.6 letters) and the 95% CI of (-0.70, 1.90) for the treatment difference was entirely within the equivalence margin of ±3 letters.

Overall, the primary analysis supports biosimilarity of CT-P42 and Eylea.

The secondary analyses (mean changes in BCVA, proportion of patients with gained and lost ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA, central subfield retinal, thickness, ≥2-step improvement from baseline in ETDRS DRSS) were also similar between the treatment groups in most cases.

Safety

The safety profile of Eylea is well-established and the safety database of 174 patients treated for up to 52 weeks with CT-P42 was considered sufficient for the general evaluation of safety and immunogenicity of CT-P42 in comparison to the reference product.

Overall, the safety risks identified in the CT-P42 clinical development programme are consistent with the known safety profile of Eylea.

Incidences of adverse events were overall comparable between the two treatments. Imbalances in certain categories of adverse events were mostly within 5% between groups and do not suggest an essential difference between the treatments.

Immunogenicity

Immunogenicity of CT-P42 was evaluated in DME patients in Study CT-P42 3.1 using state-of-the-art and validated assays. The occurrence of ADAs was overall low and the observed ADA responses were comparable between the two treatments.

3.3. Uncertainties and limitations about biosimilarity

Quality

Minor analytical differences are observed in the level of deamidation, oxidation, C-terminal Lysine, isoaspartate, distribution of charge variants, glycation, glycoform distribution, aglycosylation, content of HMW variants, free thiols, and binding to FcyRI, FcyRIIb, and FcyRIIIa/b. However, considering the extend, location of the modifications, and the MoA of aflibercept an impact on clinical performance in the targeted indications is not expected.

Clinical

After the first study drug administration, the plasma concentration of aflibercept was somewhat higher in the CT-P42 group compared to the Eylea group. Large variation was observed for the PK measurements (CV for mean Cmax values ranging from 63.9% to 101.7%), which can be explained by the limited number of subjects in the PK Set and the overall low levels of free drug concentration in plasma.

The PK Set consisted of a very limited number of patients (N=23) and contained a high degree of variation. Plasma concentrations at week 0 and week 16 were evaluated for both treatments. Free aflibercept concentrations were highly variable and overall low in both treatments groups but these concentrations were far below the concentration required to half-maximally bind systemic VEGF (2.91 µg /mL).

3.4. Discussion on biosimilarity

At the quality level similarity between CT-P42 and EU-sourced Eylea could be demonstrated for many quality attributes in a comprehensive analytical similarity exercise. In particular, VEGF receptor domain related functionalities that are relevant for the MoA were demonstrated being highly similar between both products. The observed analytical differences have been adequately evaluated and are not expected to impact clinical performance of the product in the targeted indications.

With respect to clinical PK, the observed systemic aflibercept concentrations in patients' plasma were generally low and comparable with known data for the reference product. Overall, the observed plasma concentrations of free drug attest that there is no relevant systemic exposure.

Both products had comparable immunogenicity at an overall very low level, as known for the reference product.

The pivotal clinical study CT-P42 3.1 was adequately designed to demonstrate clinical equivalence between CT-P42 and the reference product Eylea, both in terms of efficacy and safety. The selected study population, consisting 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 and accepted equivalence margin of +/- 3.0 letters. Biosimilarity in terms of efficacy was further confirmed by secondary endpoints.

Incidences of adverse events were overall comparable between the two treatments. Imbalances in certain categories of adverse events were mostly within 5% between groups and are not considered to be clinically relevant. Overall, the safety risks identified in the CT-P42 clinical development programme are consistent with the known safety profile of Eylea.

3.5. Extrapolation of safety and efficacy

In the EU, the reference product Eylea is approved in adults for the treatment of nAMD, RVO, DME and myopic CNV in adults. The clinical development program for the proposed biosimilar CT-P42 comprised a single pivotal phase 3 study (CT-P42 3.1) to compare CT-P42 and Eylea regarding efficacy, safety, pharmacokinetics and immunogenicity in the treatment of subjects with DME.

The applicant applied to obtain the approval for all the therapeutic indications that are currently approved for Eylea except for ROP, namely wet AMD, CRVO, BRVO, DME and myopic CNV, based on extrapolation of data generated from Study CT-P42 3.1 in DME patients to all the other indications. The applicant did not apply to obtain the approval for CT-P42 for the treatment of retinopathy of prematurity in preterm infants, recently approved for Eylea pre-filled syringe. For the administration of aflibercept in this population, a low-volume, high-accuracy syringe or a paediatric dosing device would be required. In view of the lack of any of these, it was appropriate not to apply for the ROP indication.

The applicant justified the extrapolation of indications based on the extensively studied properties of aflibercept which are common among all the indications of Eylea and a comprehensive comparability exercise, including the mechanism of action, structural analysis, functional assays and the clinical biosimilarity of PK, efficacy, safety and immunogenicity demonstrated during the development of CT-P42.

As highlighted in a CHMP Scientific Advice (EMEA/H/SA/4380/1/2020/III), "the receptor and mechanism of action of aflibercept are the same in the different ophthalmological indications and aflibercept is delivered at its site of action. The safety and immunogenicity profile is also largely consistent between indications. Therefore, robust evidence of comparability of the test and reference products in pharmaceutical quality and a well-conducted trial in a sensitive patient population should allow extrapolation to all other indications of Eylea".

Thus, the justification presented by the applicant to allow extrapolation from DME to all approved indications of Eylea in adults was considered adequate.

3.6. Additional considerations

Off-label use is a listed important potential risk because it is adapted to Eylea. The reference product has a paediatric indication and a specific dosing device for the treatment of children. Eydenzelt is not indicated for paediatric use. Routine pharmacovigilance activities will monitor the off-label use of Eydenzelt in paediatric patients.

3.7. Conclusions on biosimilarity and benefit risk balance

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

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

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

The MAH has agreed to provide EU educational material for Eydenzelt. 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 Eydenzelt is marketed, ophthalmological clinics where Eydenzelt 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 pre-filled syringe and the vial are for single use only
- The need to expel excess volume of the syringe before injecting Eydenzelt 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 Eydenzelt

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

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