CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	BLA 761377 IND (b) (4)
Priority or Standard	Standard
Received Date(s)	June 29, 2023
PDUFA Goal Date	June 29, 2024
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Reviewer Name(s)	Rhea A. Lloyd, MD
Review Completion Date	See DARRTS stamped date
Established/Proper Name	CT-P42 (aflibercept-boav)
(Proposed) Trade Name	Eydenzelt
Applicant	Celltrion, Inc.
Dosage Form(s)	Injectable solution
Applicant Proposed Indication(s)	Same indications as those approved for US-licensed Eylea: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Applicant Proposed Dosing Regimen(s)	Same regimen approved for US-licensed Eylea: **Neovascular (Wet) Age-Related Macular Degeneration (AMD)** • The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). • Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week (monthly) dosing after the first 12 weeks (3 months). • Although not as effective as the recommended every 8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. **Macular Edema Following Retinal Vein Occlusion (RVO)** • The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)** • The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks

	(approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). • Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).
Recommendation on Regulatory Action	**COMPLETE RESPONSE**

Reviewers of Biosimilar Application

BLA 761378 Review Team Role	Reviewer
OND RPM	Dheera Semidey
CDTL	Rhea Lloyd
Clinical Reviewer	Rhea Lloyd
Pharmacology/Toxicology Reviewer	Aling Dong / Kim Hatfield
Statistical Reviewer	Sungwoo Choi
Clinical Pharmacology Reviewer	Soo Hyeon Shin/ Ping Ji
OND Labeling Reviewer	Derek Alberding
OTBB Labeling and RPM	Ruby (Chi-Ann) Wu, Jacqueline Rosenberger
OTBB Clinical Reviewer	Milalynn Victorino/ Michelle Luo
OPQ Review Team	
ATL	Sam Mindaye
RBPM	Kristine Leahy
Microbiology	Ekaterina Allen (DP)/ Holly Brevig (DS) Maxwell Van Tassell
Facility	Ekaterina Allen (DP)/ Holly Brevig (DS) Zhong Li
Comparative Analytical Assessment (CAA), Immunogenicity Assay	Hao Kiet Phan / Sam Mindaye Gunther Boekhoudt/ Sam Mindaye
Drug Substance	Hao Kiet Phan / Sam Mindaye
Drug Product	Hao Kiet Phan / Sam Mindaye
OBP Labeling	Liming Lu
OSE RPMs	Oyinlola Fashina
DMEPA Team Lead / Reviewer	Valerie Vaughn / Damon Birkmeier
OSI CSO	Roy Blay
OPDP Reviewer	Carrie Newcomer
Deputy Division Director	William Boyd
Deputy Office Director	Alex Gorovets
Office Director	Charles Ganley

Table of Contents

Glossary

Abbreviation	Definition
ADA	antidrug antibodies
AE	adverse event
AMD	Age-Related Macular Degeneration
ANCOVA	analysis of covariance
APTC	Anti-Platelet Trialists' Collaboration
ATE	Arterial thromboembolic events
BCVA	best corrected visual acuity
BDR	Blinded Data Review
BLA	Biologics License Application
BRB	blood-retinal barrier
CI	confidence interval
CMC	chemistry, manufacturing control
COVID-19	coronavirus disease 2019
CRT	central retinal thickness
CSR	Clinical study report
CST	Central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EoS	End of Study
ET	early termination
ETDRS	early treatment diabetic retinopathy study
EU	European Union
FA	Fluorescein Angiography
FAS	Full analysis set
FP	Fundus Photography
GCP	good clinical practice
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOP	intra ocular pressure
IP	investigational product
iPSP	initial Pediatric Study Plan
ITT	intent to treat
LLOQ	lower limit of quantification
LOCF	Last Observation Carried Forward
MACE	Major adverse cardiovascular events
MedDRA	Medical dictionary for Regulatory Activities
MMRM	mixed model repeated measures

NAb	neutralizing antibody
NPDR	non proliferative diabetic retinopathy
OE	ophthalmological examination
PD	Pharmacodynamic
PDR	proliferative diabetic retinopathy
PEDF	pigment epithelium derived factor
PK	Pharmacokinetic
PlGF	placental growth factor
PP	Per-protocol
PREA	Pediatric Research Equity Act
PT	Preferred term
RPE	retinal pigmented epithelium
RVO	Retinal Vein Occlusion
SAP	statistical analysis plan
SAS	safety analysis set
SCDRT	Sentinel Cohort Data Review Committee
SD	Standard deviation
SD-OCT	spectral domain - optical coherence tomography
SOC	System organ class
TEAE	treatment-emergent adverse event
USFDA	United States Food and Drug Administration
USPI	United States prescribing information
VEGF	Vascular endothelial growth factor
wAMD	wet Age-Related Macular Degeneration

1. Executive Summary

1.1. Product Introduction

Celltrion, Inc. has submitted this BLA under section 351(k) of the Public Health Service Act (PHS Act) to seek marketing authorization for CT-P42. CT-P42 has been developed as a proposed (b) (4) biosimilar product to US-licensed Eylea (hereafter referred to as US-Eylea) for intravitreal (IVT) use.

The clinical development of CT-P42 has evaluated its clinical similarity to EU-licensed Eylea with regard to efficacy, safety, pharmacokinetics and immunogenicity in the treatment of subjects with diabetic macular edema (DME). Celltrion performed a comparative analytical assessment that included three pairwise comparisons between CT-P42, US-licensed Eylea and EU-approved Eylea to establish a scientific bridge. The comparative clinical data generated using EU-approved Eylea can be used to support the assessment of biosimilarity for CT-P42 and US-licensed Eylea.

Celltrion is seeking licensure for the 2 mg (0.05 mL of 40 mg/mL) strength in a single-dose pre-filled syringe and a single-dose vial. A 2 mg (0.05 mL of 40 mg/mL) dose is for the following indications are the same as those previously approved for US Eylea:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

The Applicant is not seeking licensure for Retinopathy of Prematurity (ROP) at this time (b) (4) .

1.2. Conclusions on Clinical Similarity

Eydenzelt (also referred to as CT-P42) is recommended for approval as a biosimilar the US-licensed Eylea. The benefits and risks of aflibercept for the proposed indications have been demonstrated during the course development and approval of Eylea. In the submitted clinical study conducted for CT-P42, the primary efficacy variable, the mean change in BCVA from baseline to Week 8 between Eylea and CT-P42 and the corresponding 90% CI was well within the predefined required interval of (-3, 3). The results from this trial demonstrate that there are no clinically meaningful differences in efficacy between CT-P42 and EU-licensed Eylea in DME patients. In addition, the trial demonstrated that the safety profile between CT-P42 and EU-licensed Eylea, including adverse events, immunogenicity and PK in the tested subgroup was similar. Since DME is a sensitive indication to evaluate if any clinically meaningful differences with respect to efficacy, safety and immunogenicity exist between CT-P42 and EU-licensed Eylea. The clinical analytical assessment demonstrated the similarity between EU-approved Eylea, US-licensed Eylea and CT-P42. Therefore, this application supports the biosimilarity of CT-P42 to US-licensed Eylea.

1.3. Benefit-Risk Assessment

The data submitted by the Applicant demonstrate that the efficacy and safety of CT-P42 is similar to US-licensed Eylea. In the clinical study conducted, the primary efficacy variable, mean change in BCVA from baseline up to Week 8 was 9.43 with CT-P42 and 8.85 with EU-approved Eylea. The adjusted mean difference for mean change in BCVA from baseline to Week 8 and the corresponding 90% CI was well within the predefined Agency criteria of (-3, 3) ETDRS letters. The results of the subgroup analysis demonstrated similar results across groups. The results of this trial successfully demonstrate the similarity of CT-P42 to EU-approved Eylea.

Safety was assessed in 173 subjects treated with intravitreal injections of CT-P42 over 48 weeks. Treatment with CT-P42 is considered safe with an adverse event profile similar to US-licensed Eylea. The adverse events seen where those that are consistent with most intravitreally administered ophthalmic drugs including conjunctival hemorrhage, increase IOP, cataract, vitreous floaters and eye pain.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The following conditions if untreated will lead to visual loss: • Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy	Aflibercept has been approved to treat the listed conditions in the US and has been shown to prevent visual loss.
Current Treatment Options	Lucentis (ranibizumab injection), Eylea (aflibercept), Beovue (brolucizumab), Byooviz (ranibizumab), Macugen (pegaptanib sodium injection) and Visudyne (verteporfin for injection). Avastin (bevacizumab) is used off-label to treat nAMD.	CT-P42 will add to the armamentarium of drugs to treat several retinal diseases that lead to vision loss.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Eylea (aflibercept) is approved for the treatment of: • Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy	The results of Study CT-P42 3.1 demonstrate that CT-P42 is clinically similar to US-licensed Eylea.
Risk and Risk Management	Eylea (aflibercept) is relatively safe for the treatment of the labeled indications listed above.	The results of Study CT-P42 3.1 demonstrate that CT-P42 has a similar safety profile to US-licensed Eylea, including adverse events, immunogenicity and PK.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6 Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☒	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Diabetic retinopathy is a common cause of blindness worldwide. In 2019, approximately 463 million adults (20-79 years) were living with diabetes worldwide. DME currently affects more than 28 million people with diabetes.

Anti-VEGF drugs are effective at improving vision in people with DME. Eylea is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. US-licensed Eylea is being marketed by Regeneron Pharmaceuticals, Inc. in the US and Bayer AG in EU. CT-P42 is currently being developed as a proposed biosimilar to US-licensed Eylea in accordance with EU and US Biosimilar guidelines.

DME was selected as the study indication among all approved indications. DME is a sensitive indication to evaluate if any clinically meaningful differences with respect to efficacy, safety and immunogenicity exist between CT-P42 and EU-approved Eylea since the mechanism of action of EU-approved Eylea in DME is representative of the mechanism of action of EU-approved Eylea in all other indications for which Eylea is approved**.**

2.2. Analysis of Current Treatment Options

NDA/BLA	**Drug Name**	**Indication**
21756	Macugen (pegabtanib sodium injection)	• Neovascular (wet) age-related macular degeneration
125156	Lucentis (ranibizumab injection)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Myopic Choroidal Neovascularization (mCNV)
125387	Eylea (aflibercept)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
761202	Byooviz (ranibizumab-nuna)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Retinopathy (DR) • Myopic Choroidal Neovascularization (mCNV)
761125	Beovu (brolucizumab-dbll)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD)

NDA/BLA	Drug Name	Indication
		• Diabetic Macular Edema (DME)
761235	Vabysmo (faricimab-svoa)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Diabetic Macular Edema (DME)
761165	Cimerli (ranibizumab-eqrn)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Myopic Choroidal Neovascularization (mCNV)
21119	Visudyne (verteporfin for injection)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD)
761350	Opuviz (aflibercept-yszy)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
761274	Yesafili (aflibercept-jbvf)	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

CT-P42 (a proposed biosimilar to US-licensed Eylea) has been developed under IND 135708. It has not been approved or marketed in the US or outside the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

Celltrion met with the Agency to discuss aspects of the CT-P42 development program in the

following pre-submission meetings:

- Biological Product Development (BPD) Type 2 Meeting to obtain advice from FDA on the proposed development program to support licensure of the proposed CT-P42 product on June 22, 2020.
- BPD Type 2 to discuss development of the proposed product on August 30, 2021.
- BPD Type 2 to discuss development of the proposed product on August 15, 2022.
- BPD Type 4 meeting to discuss the format and content of the initial BLA on January 31, 2023.

3.3. Foreign Regulatory Actions and Marketing History

See Section 3.1.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspections were not requested for this application. There is no evidence of data integrity issues which suggest that the clinical trial was not conducted in compliance with good clinical practices.

4.2. Product Quality

CT-P42 drug product is formulated for intravitreal (IVT) administration as a sterile liquid solution in a pre-filled syringe (PFS) intended to deliver 2 mg of active ingredient in a 0.05 mL of solution at a nominal concentration of 40.0 mg/mL. The sterile solution is filled (b) (4) into a syringe.

CT-P42 vial drug product is formulated for intravitreal (IVT) administration as a sterile liquid solution. Each vial is designed to allow deliver of 2 mg of active ingredient in a 0.05 mL of solution at a nominal concentration of 40.0 mg/mL.

Composition of the CT-P42 Drug Product

Ingredient	Quantity[1]/Vial	Function	Grade
CT-P42 (aflibercept)	2 mg	(b) (4)	In-house
(b) (4) Histidine	0.038 mg		USP, Ph. Eur.
L-Histidine monohydrochloride monohydrate	0.033 mg		Ph. Eur.
Sodium Chloride	0.038 mg		USP, Ph. Eur.
Trehalose	5 mg		NF, Ph. Eur.

Polysorbate 20	0.015 mg	(b) (4)	NF, Ph. Eur
Water for Injection	(b) (4)		USP, Ph. Eur.

USP: United States Pharmacopeia, Ph. Eur.: European Pharmacopeia, NF: National Formulary, (b) (4)
[1] The amount of each component per vial is nominal value (labelled strength).

From the Quality Executive Summary finalized on April 15, 2024:

Recommendation and Conclusion on Approvability

Recommendation: Approval pending the outcome of pre-license inspection

Pending the outcome of the pre-license inspection (PLI), the Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761377 for CT-P42 manufactured by Celltrion, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of CT-P42 is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that CT- P42 is highly similar to US-licensed Eylea, notwithstanding minor differences in clinically inactive components. The analytical component of the scientific bridge was established to support the use of EU-approved Eylea as a comparator in clinical studies supporting this application. It is recommended that this product be approved for human use under conditions specified in the package insert.

Basis for Recommendation

a. Summary:

CT-P42 (aflibercept-oav) is developed as a proposed (b) (4) to US-licensed Eylea for the same strength, dosage form, indications, and route of administration as for the 2 mg/0.05 mL strength of US-licensed Eylea. CT-P42 is a recombinant fusion protein consisting of domain 2 from human VEGFR-1 and domain 3 from VEGFR-2 fused to the Fc portion of human IgG1. VEGF-A and placental growth factor (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, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes.

Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, which blocks the VEGFR-1 and VEGFR-2 downstream signaling cascade associated with pathological angiogenesis and vascular leakage.

Potency of the CT-P42 is assessed using two bioassays: (i) ELISA to measure its VEGF- A165 binding activity and (ii) cell-based assay to measure its VEGF blockade activity.

ELISA measures the binding of CT-P42 to VEGF-A165 coated on a plate. CT-P42 bound to VEGF-A165 are detected using a HRP conjugated rabbit anti-human IgG Fc secondary antibody. In contrast, the cell-based hVEGF blockade assay uses an HEK293 cell which contains a luciferase gene controlled by transcription factors. In the assay system, binding of VEGF-A165 binding to VEGFR on the surface of the cell results in upregulation/production of transcription factors and expression of luciferase. The presence of CT-P42 prevents binding of hVEGF-A165 to VEGFR and thus blocks expression of luciferase. All potency results are reported as percentage relative to a qualified reference material.

The totality of the CAA evidence supports that CT-P42 is highly similar to US-licensed Eylea, notwithstanding minor differences in clinically inactive components. The analytical component of the scientific bridge was established to support the use of EU- approved Eylea as a comparator in clinical studies supporting this application. The strength of 2 mg/0.05 mL CT-P42 in single-use pre-filled syringe and single dose vials was demonstrated to be the same strength as that of US-licensed Eylea. Refer to the Appendix for a summary of the CAA.

Manufacturing of CT-P42 DS is (b) (4)

The overall CT-P42 process control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for CT-P42 as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for the proposed for drug substance manufacturing (Celltrion Inc., FEI 3005241015), PFS drug product manufacturing ((b) (4)), and vial drug product manufacturing (Patheon Italia SpA, Monza, Italy; FEI# 3003065803). The proposed DS and DP manufacturing and testing facilities are under review based on the recent relevant inspectional coverage. Pending the outcome of pre-license inspection, the BLA is approvable from product quality, facility, microbiology, and sterility assurance perspectives. Individual assessments for each discipline are located in separate documents in panorama.

In addition, CDRH recommends approval for the device constituent parts of the combination product (see review by Gang Peng in panorama).

1. **Subdiscipline Recommendation:**

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assays	**-**	**Adequate**

CAA	-	**Adequate**
Facilities	-	**Pending**
Microbiology	-	**Adequate**

2. **Environmental Assessment (EA):**
Categorical exclusion is claimed by the applicant and deemed acceptable.

3. **Potency Assessment for Labeling:**
As an initial matter, we determined that no U.S. standard of potency has been prescribed for CT-P42 (i.e., there is no specific test method described in regulation for CT-P42 that establishes an official standard of potency). We next considered whether potency is a factor for CT-P42 within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for CT-P42 for purposes of § 610.61(r) because lot variability is not a concern for CT-P42 as CT-P42 manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

4. **Life-Cycle Considerations**
   a. **Established Conditions based on ICH Q12 principles:** No
   b. Drug Substance:
   - Protocols approved:
     - Stability and requalification of master cell bank (MCB) and working cell bank (WCB)
     - New WCB qualification
     - (b) (4)
     - Qualification of new primary and working reference standards
     - Requalification/stability protocol for primary and working reference standards.
     - At-scale leachables study for Container Closure System
     - Post-approval annual stability protocol and stability protocol for the extension of drug substance shelf-life
   - Residual risk: None
   - Future inspection points to consider: Refer to PLI recommendation.

c. Drug Product:
   i. Protocols approved:
      - Post-approval annual stability protocol and stability protocol for the extension of drug product shelf-life
   ii. Residual risk: None
   iii. Future inspection points to consider: Refer to PLI recommendation.

From the Integrated Quality Assessment Executive Summary Addendum finalized on June 20, 2024:

The Integrated Quality Assessment (IQA) uploaded on April 15, 2024, provided a preliminary recommendation of "approval" pending the outcome of the pre-license inspections (PLI) for the CT-

P42 drug substance manufacturer, Celltrion Inc. (Plant (b) (4) FEI 3005241015), and pre-filled syringe (PFS) drug product manufacturer, (b) (4). This IQA Addendum summarizes the outcome of these PLIs, provides the final Facilities recommendation, updates the recommendation of EYDENZELT manufacturing from sterility assurance perspective, and provides a final **complete response recommendation** from the OPQ team. The updated sections are below. Refer to the DS Celltrion June 17, 2024, PFS (b) (4) June 14 2024, and Quality Executive Summary (uploaded to DARRTS on 04/15/2024) memorandum for all other review sections.

Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761377 for EYDENZELT (aflibercept-boav) manufactured by Celltrion Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of EYDENZELT is well-controlled and will lead to a product that is pure and potent. The comparative analytical data support a demonstration that EYDENZELT is highly similar to US-licensed aflibercept. From a CMC standpoint, OPQ is recommending a **Complete Response letter be issued to CELLTRION, Inc.** to outline the deficiencies noted below and the information and data that will be required to support approval.

Microbiology

1. (b) (4)
2. (b) (4)

3. (b) (4)

4.

5. Following review of DMF (b) (4) and cross- referenced in this application, FDA conveyed deficiencies to the DMF holder. The holder should update the DMF with satisfactory responses to these deficiencies prior to your complete response to your application. Your complete response should include the date(s) of the DMF amendment. The assessment of application approvability and the resolution of DMF deficiencies would be evaluated upon receipt of the complete response. Please work with the DMF holder in resolving the related deficiencies.

Facility Inspection

1. During a recent CGMP inspection and a pre-license inspection (PLI) of Celltrion Inc. (Plant (b) (4) FEI 3005241015), the drug substance manufacturer for this application, our field investigators conveyed deficiencies to the representative of the respective facilities. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Our determination that the facility's responses are satisfactory will depend on a finding that the facility has come into compliance with CGMP and has addressed any deficiencies specific to your application. You should coordinate with the facility for timely resolution of all inspection deficiencies, as well as to determine if any deficiencies may require updates to your application. Your complete response should include the date(s) of the facility's responses(s) to the FDA Form 483. Please refer to the Compliance Program CP 7356.002 for guidance on post-inspection activities specific to GMP compliance evaluation. FDA may determine that a CGMP reinspection and/or additional PLI is needed to confirm satisfactory resolution of inspection deficiencies before this application can be approved. If both CGMP and PLI reinspection are needed, the

PLI coverage will generally occur following a determination that the facility is in compliance with CGMP.

2. Following pre-license inspection of [redacted], the pre-filled syringe drug product manufacturer listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.
3. Inspection of the [redacted] is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

Additional Microbiology comments

The following comments/recommendations were not approvability issues.
Based on the information submitted in your response to Q.20 of our information request on 03/14/2024 (Attachment 3) it appears that [redacted]. The risk of this event to DP microbial contamination is not fully understood and should be thoroughly evaluated. For example, it is not clear which [redacted], frequency and duration of this potential CCI breach or whether the event has any CCI impact.

Establishment Information:

Overall Recommendation: Withhold			
Facility name and address	**FEI**	**Responsibilities and profile code(s)**	**Status**
Drug substance			
CELLTRION, Inc. [redacted]Academy-ro, Yeonsu-gu , Incheon, N/A, Republic of Korea, 22014	3005241015	**Drug substance:** Production of CT-P42 DS; Release testing of CT- P42 DS; Stability testing of CT-P42 DS; Testing of the MCB and WCB; Storage of the MCB and WCB; Testing of CT-P42 unprocessed bulk. **Drug product** Vial: DP storage, release, and stability testing PFS: DP storage, design controls, release, and stability testing	Withhold - Based on Inspection
Bioreliance Ltd. Todd Campus, Glasgow, Lanarkshire, United Kingdom, G20 0XA	3005343934	Production of [redacted]; Testing of the [redacted]	No Evaluation Necessary

Bioreliance Ltd. Innovation Park, Hillfoots Road, Stirling, N/A, United Kingdom, FK9 4NF	3005619549	Storage of the (b) (4)	No Evaluation Necessary
BioReliance Ltd Pentlands Science Park, Penicuik, N/A, United Kingdom, EH26 0PZ	3005619544	Testing of the (b) (4)	No Evaluation Necessary
WuXi Advanced Therapies Inc., 400 Rouse Blvd, Philadelphia, PA 19112	(b) (4)	Testing of (b) (4)	Approve - Based on Previous History
Samsung Biologics 300, Songdo bio-daero , Incheon, Yeonsu-gu, Republic of Korea, 21987	3010479596	Testing of (b) (4) (b) (4)	Approve - Based on Previous History
Drug product			
Patheon Italia S.p.A Viale Gian Battista Stucchi 110, Monza, 20900, Italy	3003065803	Vial: DP manufacture, storage, release testing (endotoxin and sterility only), (b) (4) bioburden and endotoxin testing.	Approve - Based on Previous History with Post-Approval Inspection (PoAI) follow up
STERIPACK MEDICAL POLAND SP. Z O. O. Ul. Japonska 1, Leg, 55-220, Poland	3007766601	Vial: secondary packaging (labeling and cartoning), incoming controls of vial kit device components PFS: cartoning and storage of fDP	No Evaluation Necessary
CELLTRION Pharm, Inc. 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea	3012279978	Vial: secondary packaging (labeling and cartoning) PFS: cartoning and storage of fDP	
(b) (4)			Withhold - Based on Inspection
			Approve - Based on Previous History
			PLI recommended
			Approve - Based on Previous History
Sterigenics Belgium Petit-Rechain S.A Avenue André Ernst 21 B-4800 Petit-Rechain (Verviers), Belgium	3002807111	PFS: (b) (4) sterilization	Approve - Based on Previous History
Sterigenics Germany GmbH Kasteler Str. 45, 65203 Wiesbaden, Germany	3006003617	PFS: release testing of (b) (4) sterilized DP (sterility of syringe only)	Approve - Based on Previous History

Facilities:

Celltrion Inc. ([(b) (4)] Plant [(b) (4)] FEI 3005241015) is responsible for the manufacture of CT-P42 drug substance. In addition, the facility was responsible for part of the comparative analytical assessment. While Patheon Italia SpA, (FEI# 3003065803) is responsible for the manufacture of the vial drug product presentation, [(b) (4)] is proposed to manufacture the pre- filled syringe drug product. The commercial filling line proposed for the PFS filling was [(b) (4)].

Celltrion Inc. was previously inspected in May 2022 by CDER in support of BLA 761268 for CTP16 DS and DP manufacture, and BLA 761091 for CTP13 DS manufacture in Plant [(b) (4)]. The PLI was Categorized as VAI. A general cGMP inspection was conducted by ORA in October 2019. Plant [(b) (4)] was currently undergoing expansion and improvement activities. Furthermore, PLI was conducted in August 2018 by CDER in support of BLA 761088 (CPT10, biosimilar to Rituxan) in Plant [(b) (4)] and BLA 761091 (CPT6, biosimilar to Herzuma) DS manufacturing (CBI) in Plant [(b) (4)], which was categorized as VAI. [(b) (4)] is a newly renovated suite within Celltrion Plant [(b) (4)] facility ([(b) (4)]). Celltrion confirmed that there is no history of GMP inspection associated with the [(b) (4)] within Plant [(b) (4)].

A pre-license inspection and a CGMP inspection of Celltrion Inc., facility (FEI: 3005241015) were conducted from 2/19/2024-2/27/2024. Significant deficiencies were observed in the quality system related to the manufacture of CT-P42 drug substance. At the conclusion of the inspection, form 483 with 10 observations was issued to the firm. The identified issues include: (1) procedures designed to prevent microbiological contamination of products purporting to be sterile did not include adequate validation of the [(b) (4)] process, (2) inadequate biosafety testing laboratory operation, (3) lack or not following procedures designed to prevent microbiological contamination of sterile products, (4) responsibilities and procedures pertaining to the Quality Unit are not in writing or fully followed, (5) lack of assurance that DS manufacturing operations in Building [(b) (4)] are appropriately designed to prevent contamination and cross-contamination of the products manufactured in the facility, (6) written records of investigations into unexplained discrepancies do not always include appropriate conclusions and follow-up, (7) Quality Unit is not fully exercising its authority and/or responsibilities to provide adequate oversight throughout GMP manufacturing operations, (8) lack of appropriate controls over computers or related systems, (9) deficient calibration verification of laboratory instruments used in routine analysis. At the time of original IQA summary write up, Celltrion Inc., facility (FEI: 3005241015) had a pending Official Actions Indicated (pOAI) alert based on PLI observation and the ORA compliance review was ongoing. On June 12, 2024, ORA completed their compliance review and recommended OAI status. This addendum memo was written to finalize the facility assessment section of the review.

The pre-license inspection on the DP manufacturing site at [(b) (4)] was conducted from [(b) (4)] to [(b) (4)], in support of BLA 761377 (Aflibercept, applicant Celltrion) DP manufacture and BLA [(b) (4)] DP manufacture. At the conclusion of the inspection, form 483 with 9 observations was issued to the firm with. The identified issues include [(b) (4)]

[redacted] The initial field recommendation for BLA 761377 was "withhold" due to the objectionable conditions related to [redacted] practices and facility design. The recommendation was upheld during compliance review.

In addition, an inspection of the [redacted] facility (FEI# [redacted]) is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

Final facility recommendation:
Withhold- based on Inspection and sterility assurance issues.

4.3. Clinical Microbiology

Not applicable to this application.

4.4. Nonclinical Pharmacology/Toxicology

No relevant nonclinical studies were performed.

4.5. Clinical Pharmacology

From the Clinical Pharmacology review finalized on March 18, 2024:

The Office of Clinical Pharmacology has reviewed clinical pharmacology data submitted for BLA 761377 and recommends approval of this BLA from a clinical pharmacology perspective. The key review issues with specific clinical pharmacology recommendations and comments are summarized below.

Review Issue	Recommendations and Comments
PK similarity	Systemic exposures of CT-P42 and EU-Eylea evaluated in a subset of subjects (n=23) with DME in Study CT-P42 3.1 were generally comparable based on descriptive statistics, supporting a demonstration of no clinically meaningful differences between CT-P42 and EU-Eylea. The use of EU- Eylea to support biosimilarity between CT-P42 and US-Eylea was established via comparative analytical assessments (see Section 2 for more details). Therefore, PK similarity between CT-P42 and US-Eylea is supported by the PK data from the Study CT-P42 3.1.
PD similarity, if applicable	Not applicable

Immunogenicity assessment	Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between the CT-P42 and the EU-Eylea in subjects with DME in Study CT-P42 3.1 supports no clinically meaningful differences between CT- P42 and US-Eylea.

There are no residual uncertainties regarding the PK and immunogenicity assessment of CT-P42 in this submission from a clinical pharmacology perspective.

4.6. Devices and Companion Diagnostic Issues

See the completed CDRH review.

4.7. Consumer Study Reviews

Not applicable to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Overview of CT-P42 Clinical Development Program

Study	Design	Objectives and Endpoints	Treatment	Results
CT-P42 3.1 (Comparative efficacy and safety study) **Ongoing** (W24 CSR CT-P42 3.1)	Phase 3, double-masked, randomized, active controlled, parallel group study to compare efficacy and safety of CT-P42 and EU-Eylea in patients with DME	**Primary:** To demonstrate that CT-P42 was similar to EU-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-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-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**	**Clinical Pharmacology** 5. **PK** CTD Section 2.5-3.1 6. **Immunogenicity** CTD Section 2.5-3.4 CTD Section 2.7.2.4-5 **Efficacy** CTD Section 2.5-4.5 **Safety** CTD Section 2.5-5 **Usability** CTD Section 2.5-6

[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; ETDRS, Early Treatment of Diabetic Retinopathy Study

Reviewer's Comment: *In the June 22, 2020, BPD Type 2 meeting, Celltrion asked the Agency about the acceptability of using European Union- approved Eylea as the reference product for the proposed clinical study (CT-P42 3.1). The Agency responded:*

> *If the results from the comparative analytical assessment that includes three pairwise comparisons between CT-P42, US-licensed Eylea and EU-approved Eylea are adequate, and establish a scientific bridge, we agree that the comparative clinical data generated using EU-approved Eylea can be used to support the assessment of biosimilarity for CT-P42 and US-licensed Eylea.*

5.2.Review Strategy

The clinical development program involves a single clinical study to demonstrate the similarity of CT-P42 to EU-Eylea (aflibercept). The clinical study evaluated the similarity of CT-P42 and EU-licensed Eylea in subjects with Diabetic Macular Edema.

Efficacy was compared using the primary endpoint of mean change in BCVA at Week 8 between CT-P42 and EU-licensed Eylea. Similarity was demonstrated if the treatment difference of mean change in BCVA, from baseline to Week 8 based on 90% CI was fully contained within the interval (-3, 3).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1.1. Study CT-P42 3.1

Primary Objective:
To demonstrate that CT-P42 was similar to Eylea in terms of efficacy as determined by clinical response according to the mean change from baseline at Week 8 in Best Corrected Visual Acuity (BCVA) using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.

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

Trial Design:
Study CT-P42 3.1 is a randomized, active-controlled, double-masked, parallel-group, and multicenter 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 through Week 52. The Main Study period was 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.

There were 3 study periods in this study:

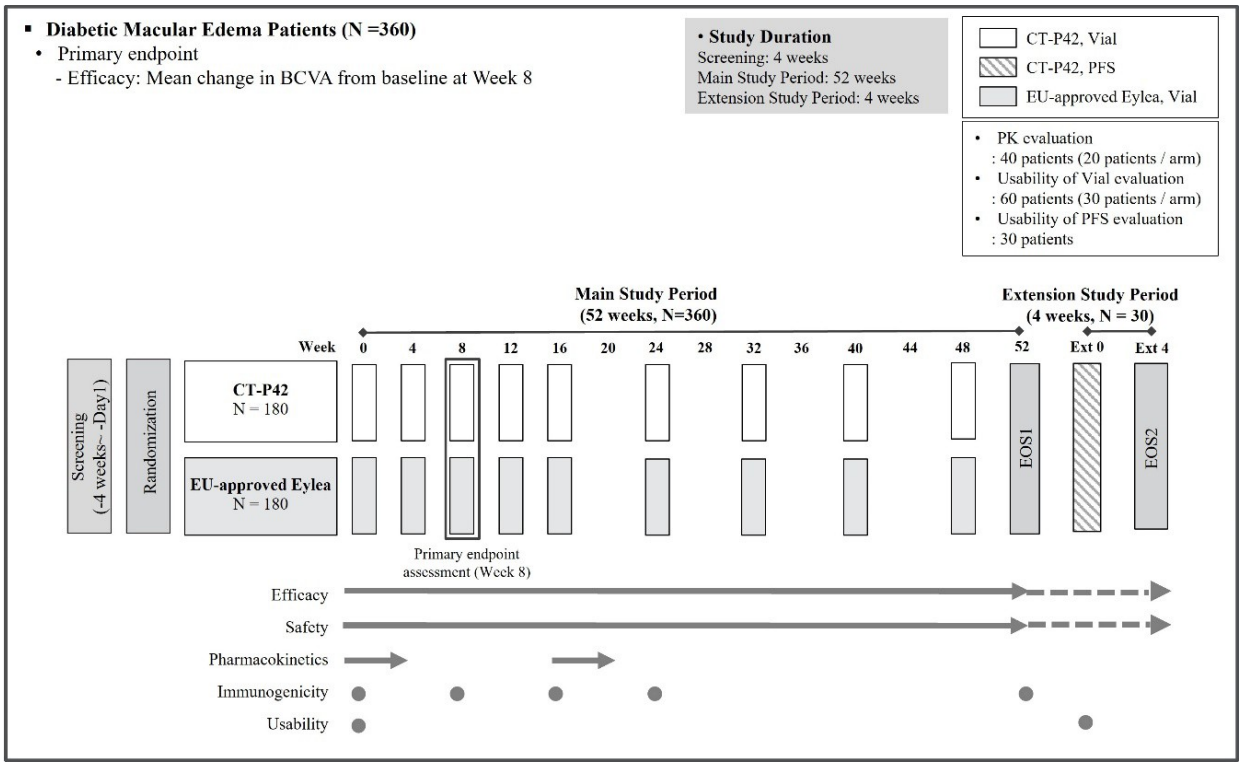
- Screening Period: Day −28 to Day −1
- Main Study Period: Week 0 to Week 52 (the first end-of-study visit)
- Extension Study Period (4 weeks): Pre-filled Syringe open-label evaluation (the second end-of-study visit)

During the Screening Period, the eligibility of the patients for study enrollment was checked. During the Main Study Period, the patients were administered CT-P42 or Eylea in a 1:1 ratio via IVT injection using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses. The randomization to treatment assignment was stratified as follows: BCVA score (<55

letters versus ≥55 letters) using the ETDRS chart on Day 1; country; and PK subgroup (Yes versus No).

After the completion of the Main Study Period, approximately 30 patients are planned to enter the Extension Study Period to receive 1 additional dose of CT-P42 via IVT injection using a single-dose PFS at Extension Week 0 regardless of the treatment group in the Main Study Period.

After all randomized patients' 24-week data was available, this first clinical study report (CSR) was prepared on the unmasked study data as planned. The results were generated by the predefined unmasked personnel from Sponsor and contract research organization including data up to Week 24 of the Main Study Period for each patient. The randomization codes for the Main Study Period will not be revealed to patients, investigators, and predefined masked study center personnel until all patients complete the study and the database lock for the final CSR, except for predefined unmasked personnel from Sponsor and contract research organization. The final CSR will include the analyses of all data up to Week 52 of the Main Study Period, and up to Week 4 of the Extension Study Period.
The study design and patient assessment overview are presented in the figure below.



Abbreviations: BCVA, best corrected visual acuity; EOS, end-of-study; Ext 0, Extension Week 0; Ext 4, Extension Week 4

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' in this study. 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 EOS1 visit.

The clinical efficacy data up to Week 24 of Main Study Period from Study CT-P42 3.1 in patients with DME were included in the original submission.

List of Investigators
This study was conducted at 83 sites in Czech, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Russia, Slovakia, Spain, Ukraine, Republic of Korea, and India. The global principal investigator was Professor David Mark Brown, Retina Consultants of Houston, 6560 Fannin St, Ste 750 Houston, Texas 77030-2727, United States.

Investigator	**Site Number**	**Site Address**	**Randomized Subjects**
Czech Republic			
Jan Hamouz	3501	Ocni klinika FNKV Srobarova, 1150/50, Praha 10, 10034 Czech Republic	2
Bohdan Kousal	3502	VFN Ocni klinika U Nemocnice 2, Praha 2, 12808 Czech Republic	5
Vladimir Korda	3503	OFTEX, s.r.o. Rokycanova 2798, Budova polikliniky, Pardubice, 53002 Czech Republic	3
Miroslav Veith	3504	Faculty Hospital Kralovske Vinohrady, Oftalmology Clinic Srobarova 1150, Praha 10, 10034 Czech Republic	14
Jaroslava Dusová	3505	Fakultni nemocnice Hradec Kralove, ocni klinika Sokolska 581, Hradec Kralove, Kralovehradecky kraj, 50005 Czech Republic	8

Investigator	Site Number	Site Address	Randomized Subjects
Jan Ernest	3506	Axon Clinical, s.r.o. Ostrovskeho 3, Praha 5, Smichov, 15000 Czech Republic	5
Estonia			
Kai Noor	3801	Silmalaser OU Katusepapi 6, Tallinn, Harjumaa county, 11412 Estonia	1
Tiia Jugaste	3803	East-Tallinn Central Hospital Ravi street 18, Tallinn, Harju county, 10138 Estonia	1
Germany			
Walter Sekundo	1802	Universitätsklinikum Gießen und Marburg Klinik für Augenheilkunde Marburg, Baldingerstraße, Marburg, Hessen, 35043 Germany	0
Hakan Kaymak	1803	Trialcare - Innovative Internationale Ophthalmochirurgie GbR c/o MVZ Oberkassel Makula Netzhaut-Zentrum Theo-Champion-Str. 1, Düsseldorf, Nordrhein-Westfalen, 40549 Germany	0
Frank G. Holz	1805	Universitaets-Augenklinik Bonn, Studienzimmer, Venusberg Campus 1 Gebäude 05, Bonn, Nordrhein-Westfalen 53127 Germany	0
Hungary			
Á gnes Kerényi	2001	Bajcsy-Zsiliniszky Hospital Ophthalmology Dept., Maglodi ut 89-91, Budapest, 1106 Hungary	5
Norbert Czumbel	2002	Jahn Ferenc Del-pesti Hospital Szemeszeti Osztaly, Koves ut 1, Budapest, 1204 Hungary	7

Investigator	Site Number	Site Address	Randomized Subjects
Alexis Tsorbatzoglou	2004	Szabolcs-Szatmar-Bereg County Hospital 68 Szent Istvan Utca, Nyiregyhaza, Szabolcs-Szatmar-Bereg, 4400 Hungary	4
Gábor Vogt	2005	MH EK Dozsa Gyorgy 112, D. epulet, 7. emelet, Budapest, 1068 Hungary	4
András Papp	2006	Semmelweis University Department of Ophthalmology 41 Maria str., 4th floor, Budapest, 1085 Hungary	12
Balázs Varsányi	2007	Ganglion Medical Center Varadi Antal u 10, fszt. 5, Pecs, Baranya, 7621	2
Hungary			
Attila Vajas	2009	University of Debrecen Nagyerdei krt 98, Ophthalmology "Szemklinika", Debrecen, 4032 Hungary	7
India			
Rupak Kanti Biswas	5101	B B Eye Foundation VIP RAA 36, VIP ROAD, RAGHUNATHPUR, Kolkata, West Bengal, 700059 India	5
George J. Manayath	5102	Aravind Eye Hospital Avinashi Road, Coimbatore, Tamilnadu, 641014 India	6
Virendra Agrawal	5103	Dr. Virendra laser Phaco Surgery Centre Tonk Phatak, Behind Toyota Car Showroom, Gandhi Nagar Tonk Road, Jaipur, Rajasthan, 302015 India	2

Investigator	Site Number	Site Address	Randomized Subjects
Sucheta Kulkarni	5104	PBMA's H V Desai Eye Hospital, Retina Department S. No 93 Tararwade Vasti, Mohammadwadi Road, Hadapsar, Pune, Maharashtra, 411060 India	3
Vipul Prajapati	5105	Government Eye Hospital, M & J Western Regional Institute of Ophthalmology Oculoplasty Department Room no 149/256, Manjushree Mill Compound, Bariya Limdi Cross Road, Asarwa, Ahmedabad, Gujarat, 380016 India	3
Santosh Gopi Krishna Gadde	5106	Narayana Netralaya 121/C, Chord Road, 1st R Block, Rajaji Nagar, Bangalore, Karnataka, 560010 India	5
Ramandeep Singh	5107	Advanced eye center PGIMER Sector 12, Chandigarh, Chandigarh, 160012 India	6
Rajpal Vohra	5108	Dr. Rajendra Prasad Centre for Ophthalmic Sciences All India Institute Of Medical Sciences, Ansari Nagar, New Delhi, 110029 India	7
Rohan Chauhan	5112	Rising Retina Clinic 312-313 Iscon Centre, Shivranjani Crossroads, Satellite, Ahmedabad, Gujarat, 3800015 India	9
Naresh Babu Kannan	5113	Aravind Eye Hospital and Postgraduate Institute of Ophthalmology Anna Nagar No 1, Madurai, Tamilnadu, 625001 India	3
Sribhargava Natesh	5114	Nethra Eye Hospital No. 8.80 feet road, RMV 2ND STAGE, Bangalore, Karnataka, 560091	5

Investigator	Site Number	Site Address	Randomized Subjects
		India	
Usha Nikumbh	5115	B J Government Medical College Sassoon General Hospitals Pune Jai Prakash Narayan Road, NEAR PUNE RAILWAY STATION PUNE, Pune,Maharashtra, 411001 India	1
Shobhana Mange	5116	Shivam Retina Clinic and Eye Hospital Majura gate, Ring Road, Surat, Gujarat, 395001 India	11
Bhavik Panchal	5117	L V Prasad Eye Institute Gmr Varalakshmi Campus, Hanumanthwaka junction, Visakhapatnam, Andhra Pradesh, 530040 India	3
Sharad Bhomaj	5118	Shanti Saroj Netralay SHANTI A N GAIKWAD ROAD, BESIDE SUNDAR NAGAR, Miraj, Maharashtra, 416410 India	4
Prabhu Shanker Mahalingam	5119	Sankara Eye Hospital Sathy Road Sivanadapuram, Coimbatore, Tamilnadu, 641035 India	1
Mahajan Sheshadri Vishnu	5120	St. Theresas Hospital Rythu Bazar Erragadda Main Road, Hyderabad, 500018 India	5
Prakash Vilakumadathil Surendranath	5121	Comtrust Eye Hospital Mini Bypass Road, Puthiyara, Calicut, Kerala, 673004 India	6
Umesh Chandra Behera	5122	LV Prasad Eye Institute MTC Campus, Patia, Bhubaneshwar, Odisha, 751024 India	3

Investigator	Site Number	Site Address	Randomized Subjects
Thomas Cherian	5124	Little Flower Hospital & Research Center SH1, Angamaly, Kerala, 683572 India	1
Lakshmi Kanta Mondal Krishnapada Baidya (Previous)	5125	Regional Institute of Ophthalmology 88, College Street, Kolkata, West Bengal, 70073 India	11
Shilpi Narnaware	5126	Sarakshi Netralaya Plot No. 19, Pragati Co-operative society, Wardha RD Rajiv Nagar, Nagpur, Maharashtra, 440025 India	4
Korea, Republic of			
Hyeong Gon Yu	5402	Seoul National University Hospital 101 Daehakro, Jongno-gu, Seoul, 03082 Korea, Republic of	0
Young Hee Yoon	5404	Asan Medical Center 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505 Korea, Republic of	1
Jae Ryung Oh	5405	Korea University Anam Hospital 73 Goryeodae-ro, Seongbuk-gu, Seoul, 02841 Korea, Republic of	11
Jae Pil Shin	5406	Kyungpook National University Hospital 130 Dongdeok-ro, Jung-gu, Daegu, 41944 Korea, Republic of Poland	1
Tomasz Żarnowski	2502	Independent Public Clinical Hospital No 1 (Samodzielny Publiczny Szpital Kliniczny nr 1) Department of Diagnostics and Microsurgery of Glaucoma, Chmielna 1, Lublin, Lubelskie, 20-079 Poland	4
Dominik Zalewski	2503	Centrum Diagnostyki i Mikrochirurgii Oka LENS Ulica Budowlana 3A, Olsztyn, Warminsko-	4

Investigator	Site Number	Site Address	Randomized Subjects
		Mazurskie, 10-424 Poland	
Ewa Mrukwa-Kominek	2505	Professor K. Gibinski University Clinical Centre Ceglana 35, Katowice, Silesian, 40-514 Poland	3
Sławomir Teper	2506	Gabinet prof. Edwarda Wylegaly Gallusa 4, Katowice, Silesian, 40-594 Poland	2
Bożena Anna Romanowska- Dixon	2507	Szpital Uniwersytecki w Krakowie Kopernika 38, Krakow, Malopolskie, 31- 501 Poland	8
Jakub Kałużny	2508	NZOZ OFTALMIKA 15 Modrzewiowa street, Bydgoszcz, Kuyavia-Pomerania, 85-631 Poland	3
Dominika Romańczak	2509	Centrum Zdrowia MDM ul. Warynskiego 10A, Warszawa, Mazowieckie, 00-631 Poland	9
Małgorzata Siewierska	2511	Szpital Sw. Rozy ul. Skotnicka 230 A, Krakow, Malopolskie, 30-394 Poland	4
Małgorzata Woś	2515	Centrum Medyczne Wos & Piwowarczyk sp.j. Dabska 18N/LU1-3, Krakow, 31-572 Poland	0
Małgorzata Zaraś	2516	Centrum Medyczne Pulawska Pulawska 49, Opthalmology, Piaseczno, 05-500 Poland	1
Marta Misiuk-Hojlo	2518	Uniwersytecki Szpital Kliniczny ul. Borowska 213, Oddzial Okulistyki, Budynek A, II pietro, Wroclaw, 50-556 Poland	1

Investigator	Site Number	Site Address	Randomized Subjects
Russian Federation			
Alena Eremina	2804	Novosibirsk Branch of FBSI IRTC 10 Kolkhidskaya street, Novosibirisk, Novosibirsk oblast, 630071 Russia	8
Andrey Yavorskiy	2805	V.P. Vykhodtsev Clinical Ophthalmological Hospital Dekabristov 41 Str, Omsk, Omsk oblast, 644024 Russia	6
Slovakia			
Ladislav Janco	2903	II. Ocna klinika SZU, F.D.Roosevelt Hospital Nam. L. Svobodu 1, Banska Bystrica, Banskobystricky Kraj, 97517 Slovakia	9
Milan Veselovský	2904	FNsP Zilina, Ocne oddelenie ul. Vojtecha Spanyola 43, Zilina, 01207 Slovakia	28
Marek Kacerik	2905	Ocna Klinika FN Legionarska 28, Trencin, 91101 Slovakia	4
Jana Stefanickova	2906	UNB Bratislava, Nemocnica Ruzinov, Klinika Oftalmologie Ruzinovska 6, Bratislava, 82606 Slovakia	6
Spain			
José Maria Ruiz-Moreno	3203	Hospital Universitario Puerta de Hierro Majadahonda Departamento de Oftalmologia, Calle Joaquin Rodrigo 2, Majadahonda, Madrid, 28222 Spain	1
Luis Emilio Pablo Julvez	3204	Hospital Universitario Miguel Servet Paseo Isabel la Católica 1-3. Edificio general, planta calle., Á rea oftalmología (Consultas al lado de la capilla), Zaragoza, Aragón, 50009 Spain	2

Investigator	Site Number	Site Address	Randomized Subjects
Roberto Gallego Pinazo	3207	Clinica Oftalvist Carrer De Russafa 19, Bajo, Valencia, Comunidad Valenciana, 46004 Spain	5
Ignasi Jürgens	3208	Institut Catala de Retina Carrer De Ganduxer 117, Barcelona, Catalonia, 08022 Spain	1
Marta Suarez Figueroa	3211	Clinica Baviera Paseo de la Castellana 20, 1ªplanta, Madrid, 28046 Spain	1
Laura Sararols Ramsay	3212	Hospital General de Catalunya Carrer Pedro i Pons, 1, OMIQ, Oftalmología, Planta 0, Sant Cugat del Valles, Barcelona, Catalonia, 08195 Spain	3
Juan Manuel Cubero Parra	3213	Hospital La Arruzafa Avenida de la Arruzafa 9, Cordoba, 14012 Spain	4
Marta S. Figueroa	3214	Clinica Baviera Paseo Echegaray y Caballero, 120, Zaragoza, Comunidad de Aragon, 50001 Spain	0
Francisco Javier Ascaso Puyuelo	3216	HOSPITAL CLINICO UNIVERSITARIO LOZANO BLESA Departamento de Oftalmología Planta 6, Avenida San Juan Bosco, 15, Zaragoza, 50009 Spain	0
Ukraine			
Olena Platonova	3402	Kherson City Clinical Hospital n.a. Afanasii and Olga Tropinin 2, Komarova str., Kherson, 73000 Ukraine	2
Investigator	**Site Number**	**Site Address**	

Investigator	Site Number	Site Address	Randomized Subjects
Andrii Serhiienko	3404	Professor's Serhienko Eye Clinic Pirogova st. 47A, BC "Izumrud", 4-5 floor, Vinnitsa, 21000 Ukraine	1
Nataliya Zavgorodnya	3405	Medical center LTD VISUS Nezalezhnoi Ukrainy Street, 34, Zaporizhzhia, Zaporizka oblast, 69032 Ukraine	8

Selection of Study Population

Patients with DME secondary to type 1 or type 2 DM were considered for enrollment in the study if they met all the inclusion criteria and none of the exclusion criteria.

For patients who met criteria in both eyes, the eye with the worst BCVA was selected as 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 was similar in clarity, the patient's non-dominant eye (if identifiable) was selected as the study eye. If neither eye was dominant, the right eye was designated as the study eye.

Inclusion Criteria

To participate in the study, patients must have met the following criteria:

1. Male or female patient aged ≥18 years.
2. Patient who had type 1 or 2 DM.
3. Patient with DME secondary to DM involving the center of the macula (defined as the optical coherence tomography [OCT] central subfield) in the study eye.
4. Patient whose central subfield retinal thickness was ≥350 μm as assessed by OCT based on central results in the study eye at Screening.
5. Patient who had 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.
6. Decrease in vision determined to be primarily the result of DME in the study eye.
7. Patient and/or his/her legally authorized representative were informed and were given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and signed the ICF before any specific procedures.
8. Female patient agreed to use highly effective methods of contraception consistent with local regulations during the course of the study and for at least 3 months following discontinuation of study drug (excluding women who were not of childbearing potential). Examples included the following:
   a) Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation
   b) Intrauterine device or intrauterine hormone-releasing system
   c) True abstinence, when this was in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods),

declaration of abstinence for the duration of exposure to investigational drug, and withdrawal were not acceptable methods of contraception.

A woman was considered of childbearing potential, following menarche and until becoming postmenopausal unless surgically sterile. Menopausal female patients had to have experienced their last period more than 1 year before the date of informed consent to be classified as not of childbearing potential. Male patient who was sexually active with a woman of childbearing potential had to agree to use highly effective method described as above or 2 acceptable methods of contraception (e.g., male or female condom AND additional hormonal or barrier contraceptive method other than condom by female partner) consistent with local regulations during the course of the study and for at least 3 months following discontinuation of study drug. Contraception was not required if either patient or his/her partner who had been surgically sterilized more than 24 weeks before the date of informed consent.

Exclusion Criteria

To participate in the study, patients must not have met any of the following criteria:

1. Patient who had only 1 functional eye, even if the eye met all other study requirements, or had and/or was 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, at the time, had or had a history (where indicated) of ocular condition including 1 or more of the following in the study eye:
   a) Active proliferative DR, or preretinal fibrosis involving the macula
   b) Aphakia
   c) Vitreomacular traction or epiretinal membrane that was expected to affect central vision
   d) Iris neovascularization, vitreous hemorrhage, 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) IOP ≥25 mmHg
   h) Spherical equivalent of the refractive error of worse than −6 diopters myopia
   i) Structural damage to the center of the macula that was likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, or organized hard exudates
   j) Concurrent and/or history of disease, other than DME, that could compromise visual acuity, required medical or surgical intervention during the study period, or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause) 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 had, or had a history (where indicated) of ocular condition including 1 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 had completely recovered from the infection on Day 1 was allowed to be enrolled at the investigator's discretion.

4. Patient who, at the time, had or had a history of (where indicated) systemic condition including 1 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 before the first study drug administration
   d) NYHA 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 before 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, contraindicated the use of the study drug or that could 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 had 1 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 (nonstudy) eye within 180 days before 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 before the first study drug administration in the study eye
   e) Laser photocoagulation (panretinal or macular) in the study eye within 90 days before the first study drug administration
   f) More than 2 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 before the first study drug administration or planned or expected during the study
   i) Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days before the first study drug administration

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

6. Patient with a hypersensitivity to immunoglobulin products, or patient who had allergies to any of the excipients or components of study drug, any other human proteins, or diagnostic process (e.g., anesthetics, topical broad-spectrum microbicides, fluorescein).
7. Female patient who was pregnant or breastfeeding.
8. Patient who, in the opinion of the investigator, should not have participated in the study.

Investigational Products

Test product, dose and mode of administration, batch numbers:

Test Product (supplied as)	Dose and Mode of Administration	Batch/Lot Numbers
CT-P42 (Vial)	2 mg/0.05 mL by intravitreal injection	2100486, 2100736, 2100811

Reference product, dose and mode of administration, batch numbers:

Reference Product	Dose and Mode of Administration	Batch/Lot Numbers
Eylea (Vial)	2 mg/0.05 mL by intravitreal injection	KT07TT9, KT0746C, KT095K0, KT097VK, KT09V4V, KT0AJTC, KT0B625, KT0B663

The test products were supplied in vial kits which contained 1 glass vial and injection components (filter needle, syringe, and injection needle).

Temporary Interruptions of Study Drugs

Temporary interruptions of study drug were considered for the following cases as per Eylea SmPC 2023 and Eylea USPI 2023. Study drugs were resumed at the investigator's discretion and dosing schedule was adjusted as described in Section 9.4.1.1 considering patient's safety.

- In the event of a retinal break in the study eye, the dose was to be withheld and could not be resumed until the break was adequately repaired.
- In the event of IOP ≥30 mmHg in the study eye, study drug could be resumed when the IOP was normalized to a safe range as determined by the investigator, either spontaneously or with treatment.
- In the event of a performed or planned intraocular surgery in the study eye, the dose was withheld within the previous or next 28 days.
- In the event of any active intraocular inflammation in the study eye, study drug was to be withheld and could not be resumed until the active intraocular inflammation was repaired adequately.
- Administration of study drug could be interrupted temporarily when the patient had ocular and/or periocular infection(s) in either eye as determined by the investigator and could not be resumed until the condition was repaired adequately.

Statistical Analysis Plan

Analysis Sets for the Main Study Period

- Intent-to-Treat (ITT): defined as all patients who are randomly assigned to receive either of the study drugs (CT-P42 or Eylea), regardless of whether or not any study drug was administered.
- Full Analysis Set defined as all patients who are randomly assigned and received at least 1 full dose of study drug during the Main Study Period. The FAS was the primary analysis set for efficacy endpoint analyses.
- Per-Protocol Set defined as all randomly assigned patients who receive all full doses of study drug up to Week 4 (total 2 injections) and have a BCVA assessment at Week 8. A major protocol deviation that affected the interpretation of study results of primary efficacy endpoint led to the exclusion from the PP set. Final determinations of the PP set were made at the masked data review meeting (DRM) before unmasking. The PP set was the supportive analysis set for efficacy endpoint analyses.
- PK Set defined as patients who receive at least 1 full dose of study drug and have at least 1 posttreatment PK concentration data in the Main Study Period. A major protocol deviation that affected the interpretation of study results of PK endpoints led to the exclusion from the PK set. Final determinations of the PK set were made at the masked DRM before unmasking. The PK set was the primary analysis set for the summary of PK data.
- Safety Set for Main Study Period was defined as all randomly assigned patients who receive at least 1 full or partial dose of study drug in the Main Study Period. The safety set for Main Study Period was the primary analysis set for the summary of safety data.
- Usability Set for Vial Kit was defined as all patients in the safety set for Main Study Period who have 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.

Analysis Sets for the Extension Study Period

All data collected on or after Extension Week 0 will be analyzed in the following analysis sets.

- Safety Set for Extension Study Period was defined as all patients who receive a full or partial dose of study drug via PFS in the Extension Study Period. The safety set for Extension Study Period will be used for the analyses of all safety and efficacy data collected on or after Extension Week 0.
- Usability Set for PFS was defined as all patients in the safety set for Extension Study Period who have evaluable usability measurements at Extension Week 0. The usability set for PFS will be used for the usability analysis of CT-P42 PFS.

Efficacy Endpoints

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoint

The following endpoints will also be assessed 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 CST from baseline as determined by spectral-domain OCT
- 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 to be assessed:

- Cmax1: maximum plasma concentration after the first study drug administration
- Cmax2: maximum plasma concentration after the fifth study drug administration
- Tmax1: time of observed maximum plasma concentration after the first study drug administration
- Tmax2: time of observed maximum plasma concentration after the fifth study drug administration

Usability Endpoints:
The following secondary usability endpoints were to be 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 to be assessed:

- Incidence and severity of adverse events (AEs) (ocular and non-ocular) including serious adverse event (SAE)s
- Incidence and severity of adverse events of special interest
- Arterial thromboembolic event (ATE)s
- 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 hemoglobin A1c (HbA1c)
- Prior and concomitant treatments
- DA) and neutralizing antibody (NAb)

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Efficacy Analysis:
The mean change from baseline in BCVA at Week 8 were analyzed using an analysis of covariance (ANCOVA) model with the baseline BCVA and country as covariates and treatment group as a factor.

The 2-sided 90% CI for the difference in the mean change from baseline in BCVA between the 2 treatment groups (CT-P42 and Eylea) were produced. Therapeutic equivalence of clinical response according to the mean change from baseline in BCVA at Week 8 was concluded if the 90% CI for the treatment difference falls entirely within the equivalence margin of – 3 letters to + 3 letters.

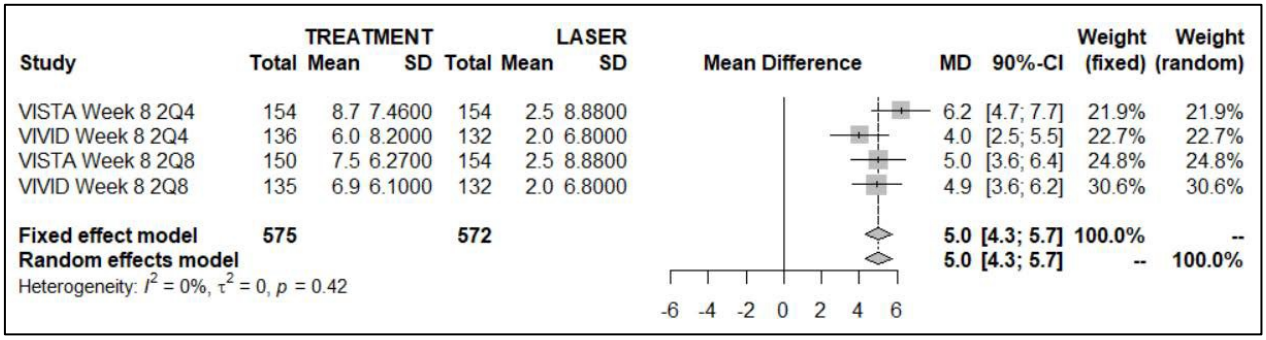
The primary efficacy analysis was conducted on the FAS, and the primary endpoint was also analyzed using the PP set as a supportive analysis. The sensitivity analysis was performed in the FAS to evaluate the impact of missing data on the primary efficacy result. Missing data was imputed using multiple imputation (MI) with the missing at random assumption. Also, the trimmed means approach was planned to be considered to address the possible bias from the potentially high and/or imbalanced missing rates in the treatment groups, however, it was not conducted as the missing rate was lower than expected.

Additionally, subgroup analyses were performed in the FAS and the PP set in the following subgroups: ADA positive or ADA negative, 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). Descriptive statistics for actual results and change from baseline of BCVA at Week 8 were generated by treatment group and the subgroups.

Equivalence Margin and Sample Size

Equivalence Margin

The calculation of the equivalence margin for the difference in mean change from baseline in BCVA was based on the 2 randomized controlled studies for the reference product (VIVID /VISTA [Brown et al., 2015]) comparing the treatment effect of Eylea with that of laser therapy in patients with DME.



The equivalence margin of ± 3 (letters) was set based on the results of the meta-analysis which indicated the lower bound of the 90% confidence interval (CI) to be 4.3 (letters) (Figure 2.5-3). Based on this estimate, a limit of ± 3 preserves about 30% as a conservative estimate of the reference product treatment effect relative to laser therapy.

PK Analysis:
The PK set was the primary analysis set for the summary of PK data.
PK analyses were performed using Phoenix WinNonlin version 8.3.4, which was validated by (b) (4). Free (vascular endothelial growth factor [VEGF]-unbound) study drug concentrations in plasma data were used to calculate Cmax1, Cmax2, Tmax1, and Tmax2 parameters by standard noncompartmental methods.
PK parameters were also summarized using descriptive statistics (n, arithmetic mean, SD, percent coefficient of variation [CV%], minimum, median, maximum, and geometric mean) and presented in the listing by treatment group.

Usability Analysis:
The usability of CT-P42 or Eylea vial kit was evaluated at Week 0. The usability of CT-P42 PFS will be evaluated at Extension Week 0 in approximately 60 patients (30 patients per treatment group) who are administered the study drug (CT-P42 or Eylea vial) at Week 0.

Safety Analysis:
All safety data, including immunogenicity, were listed and summarized by treatment group in the safety set for Main Study Period. Severity grading of AEs was recorded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All reported terms for AE and medical history were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Prior and concomitant medications were coded using the World Health Organization drug dictionary (September 2022), and the prior and concomitant nondrug therapies were coded according to the MedDRA.

Protocol Amendments

The first patient was randomized on July 22, 2021. The last patient observation was on October 14, 2022. The original protocol (version 1.0, dated 22 October 2020) was amended 3 times for global protocols.

Global Protocol Amendment, Dated 06 May 2021 (Version 2.0)
- Reference drug changed (b) (4) to EU-approved Eylea.
- Added further details of the test items for IM assessment
- Text added to clarify that inclusion criterion # 4 is about the central subfield thickness.
- Added detailed definition for a woman of childbearing potential.
- Added new conditions for temporary interruption of the study drug.
- Added detailed procedure about using independent reading center for 12-lead ECG assessment.

Global Protocol Amendment, Dated 14 January 2022 (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.

Global Protocol Amendment, Dated 12 April 2022 (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.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the principles of ICH GCP, applicable regulatory requirements, and Sponsor/CRO Standard Operating Procedures. The study followed the recommendations of ICH GCP R2 with quality oversight provided by the sponsor to ensure human subject protection and reliability of trial results.

Analysis Sets (All Randomized 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	173	175	348
Usability set for Vial kit	45	50	95

Note: Patients are classified to either treatment group according to the randomization.
Abbreviations: FAS, full analysis set; ITT, intent-to-treat; N, number of patients in the respective group; n, number of patients within a specific category; PK, pharmacokinetic; PP, per-protocol.
Source: Post-text Table 14.1.3.

Patient Disposition

	CT-P42 (N=173)	Eylea (N=175)	Total (N=348)
Total number of patients, n			
Screened[1]			484
Screening failure			136
Primary reason for screening failure[2]			
Inclusion/exclusion criteria not met			119
Patient withdrew consent			15
Lost to follow-up			1
Other			1
Randomized, n (%)	173	175	348
Initiated the study treatment for the Main Study Period	173 (100.0%)	175 (100.0%)	348 (100.0%)
Continuing the Study at Week 24	168 (97.1%)	167 (95.4%)	335 (96.3%)
Discontinued early from the study on or before Week 24	5 (2.9%)	8 (4.6%)	13 (3.7%)
Primary reason for study discontinuation, n (%)			
Adverse event	2 (1.2%)	2 (1.1%)	4 (1.1%)
Protocol deviation	0	1 (0.6%)	1 (0.3%)
Lost to follow-up	1 (0.6%)	1 (0.6%)	2 (0.6%)
Investigator decision	0	1 (0.6%)	1 (0.3%)
Withdrawal by patient	2 (1.2%)	3 (1.7%)	5 (1.4%)
Time on study prior to discontinuation (days)[3]			
n	5	8	13
Mean	64.8	41.3	50.3
SD	38.2	31.2	34.6
Minimum	27	1	1
Median	64.0	44.5	56.0
Maximum	113	91	113

Abbreviations: ITT, intent-to-treat; N, number of patients in the respective group; n, number of patients within a specific category.

1. This included screening failures and randomized patients.
2. This summary included screening failures only.
3. Only for patients who initiated the study and were prematurely discontinued from study on or before the Week 24 of the Main Study Period calculated as (Date of the last administration – Date of the first administration +1).

Source: Post-text Table 14.1.1.

Reviewer's Comments: *Similar percentages of patients in the CT-P42 and Eylea treatment groups continued on Study after Week 24, 97.1% and 95.4%, respectively.*

The number of patients discontinued prior to Week 24 was 2.9% and 4.6%, respectively for the CT-P42 and Eylea treatment groups. The primary reason for study discontinuation was the same for both treatment groups, adverse events and withdrawal by patient.

Protocol Violations/Deviations

The most frequently reported major protocol deviation was nonadherence to Inclusion/ Exclusion (I/E) criteria which affected primary efficacy result (3 [1.7%] patients in the CT-P42 group and 3 [1.7%] patients in the Eylea group). Another major protocol deviation reason was receipt of prohibited therapy which affected primary efficacy result for 1 (0.6%) patient in the Eylea group.

No cases of mis-randomization up to Week 4 or significant GCP noncompliance were reported.

Major Protocol Deviations (Randomized Patients)

	CT-P42 (N=173)	Eylea (N=175)	Total (N=348)
Major protocol deviations, n (%)			
Significant GCP non-compliance	0	0	0
Mis-randomization up to Week 4	0	0	0
Non-adherence to I/E criteria which affected primary efficacy result[1]	3 (1.7%)	3 (1.7%)	6 (1.7%)
Receipt of prohibited therapy which affected primary efficacy result[2]	0	1 (0.6%)	1 (0.3%)

Note: Percentages are calculated by using the number of all randomly assigned patients as the denominator. Patients are classified to either treatment group according to the randomization.
Abbreviations: GCP, Good Clinical Practice; I/E criteria, inclusion or exclusion criteria; N, number of patients in the respective group; n, number of patients within a specific category; CST: central subfield thickness; BCVA: best corrected visual acuity; PDR: proliferative diabetic retinopathy.

1. Two patients ((b) (6) [CT-P42 group], (b) (6) [Eylea group]) did not meet the inclusion criteria #4 which requires a baseline CST of ≥350 µm. Two patients ((b) (6) [CT-P42 group], (b) (6) [Eylea group]) did not meet the inclusion criteria #5 which requires baseline BCVA score of 73 to 34. Patient (b) (6) in CT-P42 group was founded active PDR in the study eye during the screening and met the exclusion criteria #2a. Patient (b) (6) in the Eylea group had experience of prior use of Bevacizumab in the study eye and met the exclusion criteria #5b. Details of deviation were presented in Data Listing 16.2.2.2.
2. Patient (b) (6) received ranibizumab in the fellow eye at Week 0 for the treatment of diabetic macular edema Source: Post-text Table 14.1.4.

Summary of Demographic and Stratification Data

	CT-P42 (N=173)	Eylea (N=175)	Total (N=348)
Demographics			
Age (years)			
n	173	175	348
Mean	62.5	62.9	62.7
SD	9.6	10.3	10.0
Minimum	32	25	25
Median	63.0	63.0	63.0
Maximum	85	86	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 (%)			
Surgically sterilized	5 (7.5%)	8 (10.3%)	13 (9.0%)
Postmenopausal	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 (%)			
Asian	61 (35.3%)	63 (36.0%)	124 (35.6%)
White	112 (64.7%)	112 (64.0%)	224 (64.4%)

	CT-P42 (N=173)	Eylea (N=175)	Total (N=348)
Ethnicity, n (%)			
Hispanic or Latino	5 (2.9%)	5 (2.9%)	10 (2.9%)
Nonhispanic or Nonlatino	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	19 (11.0%)	18 (10.3%)	37 (10.6%)
Former	33 (19.1%)	33 (18.9%)	66 (19.0%)
Screening value of height (cm)			
n	173	175	348
Mean	165.93	166.56	166.25
SD	9.68	9.19	9.43
Minimum	145.0	145.0	145.0
Median	164.00	167.00	166.50
Maximum	197.0	190.0	197.0
Screening value of weight (kg)			
n	173	175	348
Mean	78.25	76.85	77.55
SD	19.30	15.78	17.61
Minimum	39.3	44.0	39.3
Median	75.00	75.00	75.00
Maximum	147.0	126.0	147.0
Baseline HbA1c[2], n (%)			
≤ 8%	113 (65.3%)	116 (66.3%)	229 (65.8%)
> 8%	60 (34.7%)	57 (32.6%)	117 (33.6%)
Stratification Details Country, n (%)			
Czechia	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%)
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%)

Abbreviations: BCVA, Best Corrected Visual Acuity; ITT, intent-to-treat; N, number of patients in the respective group; n, number of patients within a specific category; PK, pharmacokinetic.; SD, standard deviation

1. Percentages were calculated by using the number of female patients.
2. Eligibility of baseline HbA1c for two patients ((b) (6)) was confirmed using local laboratory due to the War in Ukraine. These cases were reported as protocol deviation and presented in Data Listing 16.2.2.3.

Source: Post-text Table 14.1.6.

Reviewer's Comment:
The overall demographic characteristics of the subjects enrolled in this study were reasonably well balanced.

Summary of Baseline Ophthalmologic Characteristics - ITT

	CT-P42 (N=173)	Eylea (N=175)
BCVA score at Baseline		
n	173	175
Mean	60.3	60.4
SD	9.7	10.1
Minimum	34	34
Median	62.0	62.0
Maximum	73	73
ETDRS DRSS score at Baseline, n (%)		
10	1 (0.6%)	2 (1.1%)
20	3 (1.7%)	1 (0.6%)
35	58 (33.5%)	60 (34.3%)
43	48 (27.7%)	48 (27.4%)
47	25 (14.5%)	21 (12.0%)
53	16 (9.2%)	18 (10.3%)
61	7 (4.0%)	5 (2.9%)
65	3 (1.7%)	4 (2.3%)
71	1 (0.6%)	5 (2.9%)
75	0	0
81	0	0
85	0	0
90	11 (6.4%)	11 (6.3%)
CST at Baseline (μm)^2		
n	172	174
Mean	499.3	483.7
SD	138.0	111.5
Minimum	269	274
Median	465.5	462.5
Maximum	1030	842
IOP at Baseline (mmHg)		
n	173	175
Mean	16.0	15.8
SD	2.8	2.7
Minimum	7	9
Median	16.0	16.0
Maximum	22	24

Abbreviations: BCVA, Best Corrected Visual Acuity; CST, central subfield thickness; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment of Diabetic Retinopathy Study; IOP, intraocular pressure;

N, number of patients in the respective group; n, number of patients within a specific category; PD: protocol deviation.

1. The summary of BCVA score, DRSS score and CST at baseline was based on the FAS, and the summary of IOP at baseline was based on the safety set for Main Study Period. The number of patients in each group are the same among ITT, FAS, and safety set for the Main Study Period.
2. Baseline CST values could not be generated for 2 patients (patient (b) (6) in the CT-P42 group and patient (b) (6) in the Eylea group) due to the major PD. Details of deviation is presented in Data Listing 16.2.2.2.

Source: Post-text Table 14.2.1.2, Post-text Table 14.2.3.1, Post-text Table 14.2.2.1, and Post-text Table 14.3.6.6

Reviewer's Comment:
Baseline ophthalmic characteristics were similar between groups.

Summary of Diabetes Mellitus and Diabetic Macular Edema History (ITT Set)

	CT-P42 (N=173)	Eylea (N=175)	Total (N=348)
Total number of DM history	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
Mean	13.5990	14.0202	13.8108
SD	8.8011	9.5446	9.1717
Minimum	0.085	0.104	0.085
Median	13.2074	12.3450	13.0883
Maximum	38.973	40.920	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	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 one 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 one Prior Nondrug Therapy for DME, n (%)			
Laser photocoagulation	15 (8.7%)	15 (8.6%)	30 (8.6%)
Number of patients with No prior treatment for DME	157 (90.8%)	160 (91.4%)	317 (91.1%)

	CT-P42 (N=173)	Eylea (N=175)	Total (N=348)
Duration of DME (years)[1] n	173	175	348
Mean	0.5913	0.8395	0.7161
SD	1.4285	1.9134	1.6919
Minimum	0.000	0.000	0.000
Median	0.1451	0.1807	0.1684
Maximum	14.185	14.346	14.346
Baseline HbA1c[2], n (%) ≤ 8%	113 (65.3%)	116 (66.3%)	229 (65.8%)
> 8%	60 (34.7%)	57 (32.6%)	117 (33.6%)

Abbreviations: DM, diabetes mellitus; DME, diabetic macular edema; HbA1c, hemoglobin A1c; ITT, intent-to-treat; N, number of patients in the respective group; n, number of patients within a specific category; OD, oculus dexter (right eye); OS, oculus sinister (left eye); VEGF, vascular endothelial growth factor.

1. Durations of DM and DME were calculated as ([the first administration date of study drug – start date of disease]/365.25).
2. A prior medication for DME other than Intravitreal anti-VEGF and Intravitreal Steroid is summarized as 'Other medication'.
3. Eligibility of baseline HbA1c for two patients ((b) (6)) was confirmed using local laboratory due to the War in Ukraine. These cases were reported as protocol deviation and presented in Data Listing 16.2.2.3.

Source: Post-text Table 14.1.7.

Reviewer's Comments:

Diabetes mellitus and diabetic macular edema history were similar between groups. HbA1c values were consistent between treatment groups.

Efficacy Results – Primary Endpoint

Analysis of Mean Change from Baseline in BCVA at Week 8 by Treatment – (ANCOVA) (FAS and PP Set)

Treatment	n	LS Mean (SE)	Estimate of Treatment Difference in LS Means (CT-P42 – Eylea)	90% CI
FAS				
CT-P42	169	9.43 (0.798)		
Eylea	172	8.85 (0.775)	0.58	(-0.52, 1.67)
PP Set				
CT-P42	165	9.22 (0.837)		
Eylea	167	8.84 (0.840)	0.38	(-0.70, 1.45)

Abbreviations: ANCOVA, analysis of covariance; BCVA, Best Corrected Visual Acuity; FAS, full analysis set; LS, least squares; n, number of patients with BCVA score at Week 8; PP, per-protocol; SE, standard error.
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 study eye.
Source: Post-text Table 14.2.1.1.

Reviewer's Comments:
The 90% CI for the estimate of treatment difference in LS means in the PP set also falls within the equivalence margin of ± 3 letters as shown in FAS (90% CI: [-0.70, 1.45] for PP set).

Similarity was demonstrated between CT-P42 and US-licensed Eylea. The treatment difference of mean change in BCVA, from baseline to Week 8 based on 90% CI was fully contained within the interval (-3, 3).

Descriptive Statistics for Actual Value and Change from Baseline of BCVA at Week 8 by Subgroup (FAS)

	CT-P42 (N=173)		Eylea (N=175)	
Subgroup	**Actual**	**Change From**	**Actual**	**Change From**
Statistic	**Result**	**Baseline**	**Result**	**Baseline**
ADA Positive Subgroup				
n	3	3	2	2
Mean	78.3	10.7	86.5	14.5
SD	13.5	11.0	2.1	0.7
ADA Negative Subgroup				
n	164	164	164	164
Mean	68.8	8.6	68.3	7.8
SD	11.7	6.2	11.0	6.3
Age <65 years				
n	97	97	92	92
Mean	69.6	9.4	68.2	8.5

	CT-P42 (N=173)		Eylea (N=175)	
Subgroup	**Actual**	**Change From**	**Actual**	**Change From**
Statistic	**Result**	**Baseline**	**Result**	**Baseline**
SD	11.4	6.2	11.9	6.0
Age ≥65 years				
n	72	72	80	80
Mean	68.3	7.5	68.9	7.4
SD	12.3	6.1	10.2	6.6
Male				
n	104	104	96	96
Mean	70.5	9.7	69.6	8.3
SD	11.1	6.6	10.8	6.8
Female				
n	65	65	76	76
Mean	66.7	7.0	67.1	7.6
SD	12.5	5.2	11.3	5.5
Asian				
n	59	59	62	62
Mean	65.4	7.7	64.5	7.6
SD	9.5	5.4	10.5	5.6
White				
n	110	110	110	110
Mean	71.0	9.1	70.8	8.2
SD	12.4	6.5	10.8	6.6
Baseline HbA1c ≤8%				
n	109	109	113	113
Mean	69.5	8.9	69.1	8.0
SD	12.0	6.6	11.0	6.7
Baseline HbA1c >8%				
n	60	60	57	57
Mean	68.2	8.2	67.6	8.0
SD	11.4	5.5	11.2	5.5
Baseline BCVA <40 letters				
n	9	9	6	6
Mean	42.6	5.9	47.7	11.2
SD	6.8	6.7	8.7	7.3
Baseline BCVA ≥40 to <55 letters				
n	38	38	39	39
Mean	57.6	7.3	57.2	9.3
SD	8.0	6.9	8.7	8.1
Baseline BCVA ≥55 to <65 letters				
n	52	52	52	52
Mean	71.0	10.7	66.9	7.4
SD	6.3	5.9	6.2	5.5
Baseline BCVA ≥65 letters				
n	70	70	75	75
Mean	77.3	8.2	77.2	7.5
SD	5.8	5.6	5.8	5.5

The results of the subgroup analyses on the change from baseline in BCVA at Week 8 were generally similar between the CT-P42 group and the Eylea group. While numerical differences were observed between the subgroups, these differences were derived from relatively small number of the patients and the results did not indicate any clinically significant trend.

Reviewer's Comment:
There were no significant differences in the primary efficacy results within subgroups.

Analysis of Usability
The use of the vial kit was evaluated at Week 0 in 95 injection procedures. All injections with vial kit at Week 0 were successfully administered without any use errors or close calls in both treatment groups.

Data Quality and Integrity

The application was of sufficient quality to conduct a substantive review of the data. There were not data integrity issues uncovered during the review of this NDA.

7. Review of Safety

7.1. Safety Review Approach

The safety of CT-P42 was evaluated in in a single randomized, double-masked, active-controlled study compared to US-licensed Eylea in patients with diabetic macular edema. The safety population included 348 subjects treated for 48 weeks and included all randomized subjects who received at least 1 full or partial dose of study drug.

The 4-Month Safety Update which is reviewed here includes all safety and immunogenicity data collected up to Week 52 of Main Study period (the first End-of-Study [EOS1]) and up to Extension Week 4 of Extension Study Period (the second End-of-Study [EOS2]) with the cut-off date of April 24, 2023 (last patient last visit).

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The Safety Set for Main Study Period includes 348 patients with DME (174 patients each in the CT-P42 and EU-Eylea group). The number of Safety Set for Main Study Period in each group has been updated from 173 and 175 patients in the CT-P42 and EU-Eylea groups, respectively with Patient (b) (6) who was randomly assigned to the EU-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

After the completion of Main Study Period, 31 patients with DME (15 and 16 patients in the CT-P42 and EU-Eylea groups, respectively in Main Study Period) entered into Extension Study Period for evaluation of PFS usability (4-Month Safety Update Table 14.1.11e). 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 from Safety Set for Extension Study Period from 31 patients with DME in Study CT-P42 3.1 are included.

Number of Patients Who Received the Study Drug (CT-P42, EU-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-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

Source: 4-Month Safety Update Table 14.1.11

7.2.2. Relevant characteristics of the safety population:

Refer to section 6.1.2 for demographic data.

7.2.3. Adequacy of the safety database:

The size of this database and the clinical evaluations conducted during development were adequate to assess the safety profile of this intravitreally administered biologic product.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

This BLA submission was of sufficient quality to perform a substantive review of this product.

7.3.2. Categorization of Adverse Events

All AEs (both ocular and non-ocular) were coded using MedDRA Version 23.0 or higher. An AE was considered a treatment emergent adverse event (TEAE) if it occurred or worsened on or after receipt of the first dose of study drug. AEs have been summarized using the MedDRA preferred term (PT) as event category and/or MedDRA primary system organ class (SOC) as summary category.

7.3.3. Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns of intravitreally administered products (i.e., biomicroscopy, fundoscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the trials for this product. Refer to schedule of events in section for procedures and scheduled assessments for laboratory evaluations.

7.4. Safety Results

7.4.1. Deaths

Deaths during Main Study Period (Safety Set for Main Study Period)

Patient No.	Age/ Sex/ Race	Date of First/Last Administration	Date of Death	Start Date/ Stop Date of TEAE	Preferred Term	Relationship to study drug
CT-P42 treatment group						
(b) (6)	62/M/W	(b) (6)			Dyspnea	Unrelated
	85/F/W				Cardiac arrest	Unrelated
	71/F/W				Pneumonia	Unrelated
EU-Eylea treatment group						
(b) (6)	83/M/W	(b) (6)			Death	Unrelated
	58/M/W				Death	Unrelated

Sources: 4-Month Safety Update Listings 16.2.7.1 and 16.2.7.2

7.4.2. Serious Adverse Events

No ocular serious adverse events were reported during the study.

Non-Ocular Treatment Emergent Serious Adverse Events (TESAEs) by System Organ Class and Preferred Term in Study CT-P42 3.1

(Safety Set for Main Study Period)

SOC PT	CT-P42 (N=174)	EU-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 anemia	0	1 (0.6%)
Cardiac disorders	**4 (2.3%)**	**4 (2.3%)**
Aortic valve stenosis	0	1 (0.6%)
Atrial fibrillation	0	1 (0.6%)
Atrioventricular block second degree	1 (0.6%)	1 (0.6%)
Cardiac arrest	1 (0.6%)	0
Cardiac failure	1 (0.6%)	2 (1.2%)
Coronary artery disease	0	1 (0.6%)
Myocardial infarction	1 (0.6%)	0
Ear and labyrinth disorders	**0**	**1 (0.6%)**
Deafness neurosensory	0	1 (0.6%)
Gastrointestinal disorders	**1 (0.6%)**	**1 (0.6%)**
Enterocolitis	0	1 (0.6%)
Umbilical hernia	1 (0.6%)	0
General disorders and administration site conditions	**0**	**2 (1.1%)**
Death	0	2 (1.1%)
Hepatobiliary disorders	**2 (1.1%)**	**0**
Cholecystitis	2 (1.1%)	0
Infections and infestations	**5 (2.9%)**	**4 (2.3%)**
Carbuncle	0	1 (0.6%)
Cellulitis	0	1 (0.6%)
COVID-19 pneumonia	1 (0.6%)	0
Device related infection	1 (0.6%)	0
Diabetic gangrene	1 (0.6%)	0
Emphysematous pyelonephritis	0	1 (0.6%)
Gastroenteritis	1 (0.6%)	0
Pneumonia	1 (0.6%)	1 (0.6%)
Injury, poisoning and procedural complications	**0**	**1 (0.6%)**

SOC PT	CT-P42 (N=174)	EU-Eylea (N=174)
Femoral neck fracture	0	1 (0.6%)
Metabolism and nutrition disorders	**1 (0.6%)**	**1 (0.6%)**
Diabetes mellitus inadequate control	0	1 (0.6%)
Hyponatraemia	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	**1 (0.6%)**	**0**
Vertebral end plate inflammation	1 (0.6%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (1.1%)**	**0**
Clear cell renal cell carcinoma	1 (0.6%)	0
Hepatocellular carcinoma	1 (0.6%)	0
Renal cancer	1 (0.6%)	0
Nervous system disorders	**1 (0.6%)**	**2 (1.1%)**
Carotid artery stenosis	1 (0.6%)	0
Cerebral infarction	0	1 (0.6%)
Ischemic stroke	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**2 (1.1%)**	**0**
Dyspnea	1 (0.6%)	0
Pulmonary embolism	1 (0.6%)	0
Skin and subcutaneous tissue disorders	**3 (1.7%)**	**3 (1.7%)**
Decubitus ulcer	0	1 (0.6%)
Diabetic foot	2 (1.1%)	1 (0.6%)
Diabetic ulcer	0	2 (1.1%)
Skin ulcer	1 (0.6%)	0
Vascular disorders	**1 (0.6%)**	**2 (1.1%)**
Arteriosclerosis	0	1 (0.6%)
Dry gangrene	1 (0.6%)	0
Peripheral artery occlusion	0	1 (0.6%)
Vascular occlusion	0	1 (0.6%)

Source: 4-Month Safety Update Table 14.3.1.5
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.

Reviewer's comments:
Serious adverse events of cardiac failure, cholecystitis, diabetic foot and diabetic ulcer were the only ones which occurred in more than 1 patient. Each occurred in 2 patients (1.1%).

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

TEAEs Leading to Study Drug Discontinuation by System Organ Class and Preferred Term in Study CT-P42 3.1 (Safety Set for Main Study Period)

SOC PT	CT-P42 (N=174)	EU-Eylea (N=174)
Number (%) of patients with ≥ 1 ocular TEAE in study eye leading to study drug discontinuation	**1 (0.6%)**	**1 (0.6%)**
Eye disorders	**1 (0.6%)**	**1 (0.6%)**
Age-related macular degeneration	0	1 (0.6%)
Macular ischemia	1 (0.6%)	0
Number (%) of patients with ≥ 1 ocular TEAE in fellow eye leading to study drug discontinuation	**0**	**0**
Number (%) of patients with ≥ 1 non-ocular TEAE leading to study drug discontinuation	**5 (2.9%)**	**5 (2.9%)**
Cardiac disorders	**2 (1.1%)**	**1 (0.6%)**
Cardiac arrest	1 (0.6%)	0
Cardiac failure	0	1 (0.6%)
Coronary artery disease	1 (0.6%)	0
General disorders and administration site conditions	**0**	**2 (1.1%)**
Death	0	2 (1.1%)
Infections and infestations	**1 (0.6%)**	**0**
Pneumonia	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	**0**	**1 (0.6%)**
Osteoarthritis	0	1 (0.6%)
Nervous system disorders	**0**	**1 (0.6%)**
Ischemic stroke	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**1 (0.6%)**	**0**
Dyspnea	1 (0.6%)	0
Skin and subcutaneous tissue disorders	**1 (0.6%)**	**0**
Diabetic foot	1 (0.6%)	0

Source: 4-Month Safety Update Table 14.3.1.7
Notes: The total number of TEAEs count included events which lead to study drug discontinuation for all patients in the Safety Set for Main Study Period. At each level of summarization, patients were counted once if they reported one or more events. Only the most severe event was counted.

Reviewer's Comment:
The percentage of serious TEAEs leading to IP discontinuation was low and similar between groups.

7.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Ocular TEAEs in the Study Eye Reported for at Least 2% 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-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	4 (2.3%)	6 (3.4%)
Conjunctival hemorrhage	2 (1.1%)	4 (2.3%)
Intraocular pressure increased	3 (1.7%)	4 (2.3%)

Source: 4-Month Safety Update Tables 14.3.1.2 and 14.3.1.4
Note: Only TEAEs reported for at least 1% of patients for Main Study Period in either treatment group were included.

Reviewer's Comments:
The rates of ocular adverse events were similar between the treatment groups.

Non-Ocular TEAEs Reported for at Least 2% 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-Eylea (N=174)**
Total Number of non-ocular TEAEs, n	**178**	**214**
Total number of patients with ≥ 1 non-ocular TEAE, n (%)	**86 (49.4%)**	**93 (53.4%)**
Infections and infestations	23 (13.2%)	28 (16.1%)
COVID-19	8 (4.6%)	10 (5.7%)
Influenza	1 (0.6%)	6 (3.4%)
Nasopharyngitis	9 (5.2%)	4 (2.3%)

SOC PT	CT-P42 (N=174)	EU-Eylea (N=174)
Injury, poisoning and procedural complications	0	2 (1.1%)
Contusion	0	2 (1.1%)
Investigations	5 (2.9%)	9 (5.2%)
Blood creatine phosphokinase increased	2 (1.1%)	1 (0.6%)
Blood glucose increased	2 (1.1%)	3 (1.7%)
Blood triglycerides increased	0	2 (1.1%)
C-reactive protein increased	2 (1.1%)	0
Glycosylated hemoglobin increased	0	5 (2.9%)
Metabolism and nutrition disorders	17 (9.8%)	20 (11.5%)
Diabetes mellitus inadequate control	7 (4.0%)	8 (4.6%)
Dyslipidemia	1 (0.6%)	4 (2.3%)
Hyperkaliemia	4 (2.3%)	5 (2.9%)
Skin and subcutaneous tissue disorders	**10 (5.7%)**	**3 (1.7%)**
Diabetic foot	7 (4.0%)	1 (0.6%)
Vascular disorders	**11 (6.3%)**	**16 (9.2%)**
Hypertension	11 (6.3%)	16 (9.2%)

Sources: 4-Month Safety Update Tables 14.3.1.2 and 14.3.1.4
Note: Only TEAEs reported for at least 1% of patients for Main Study Period in either treatment group were included.

Reviewer's Comments:
The rates of non-ocular adverse events were similar between the treatment groups.

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-Eylea (N=174)
Total number of ATEs, n	**8**	**10**
Number of patients with ≥ 1 ATE, n (%)	**8 (4.6%)**	**8 (4.6%)**
Blood creatine phosphokinase increased	0	1 (0.6%)

SOC PT	CT-P42 (N=174)	EU-Eylea (N=174)
Cardiac arrest	1 (0.6%)	0
Carotid artery stenosis	1 (0.6%)	2 (1.1%)
Cerebral infarction [1]	0	2 (1.1%)
Coronary artery disease	1 (0.6%)	1 (0.6%)
Death	0	2 (1.1%)
Dyspnea [3]	1 (0.6%)	0
Myocardial infarction	2 (0.6%)	0
Peripheral artery occlusion [2]	1 (0.6%)	1 (0.6%)
Pneumonia [3]	1 (0.6%)	0

Source: 4-Month Safety Update Table 14.3.1.8
1 Stroke includes cerebral infarction and ischemic stroke
2 Peripheral artery occlusion includes peripheral artery occlusion and peripheral artery occlusive disease.
3 Classified as ATEs by the Applicant.

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.

Reviewer's Comments:
The rates of arterial thromboembolic adverse events were similar between the treatment groups.

7.4.5. Laboratory Findings

The results for clinical laboratory parameters i.e., clinical chemistry, hematology, and urinalysis up to Week 24 showed no notable differences between CT-P42 and EU-Eylea groups. Consistent findings were shown in the safety data through the End-of-Study (EOS) 2.

7.4.6. Immunogenicity

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-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)		

Visit ADA Result NAb Result	CT-P42 (N=174)	EU-Eylea (N=174)
	Number (%) of patients	
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
Week 52/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%)

Sources: 4-Month Safety Update Table 14.3.6.13 and Listing 16.2.9.11
Note: The ADA test involved both screening and confirmatory assays to confirm true positive results. Samples that were potentially positive in the screening assay are spiked with excess study drug to determine if patients were a true positive, labeled 'Positive'. The NAb screening assessments were only made on samples with an ADA confirmatory assay result of 'Positive'.
[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 Main Study Period.
[2] At least one NAb positive result after the first study drug administration.
Abbreviation: N, The number of patients in the Safety Set for Main Study Period

Reviewer's Comment:
The frequency of ADA and neutralizing antibody (NAb) incidences at each timepoint was similar between the treatment groups and the proportion of ADA-positive patients at all timepoints was below 2%. No clinically meaningful difference in post-treatment ADA and Nab positive patients was observed between the 2 treatment groups.

7.4.7. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose and drug abuse potential are negligible since this product is an intravitreal injection administered by a physician. Withdrawal and rebound have not been studied.

7.5 Safety Analyses by Demographic Subgroups

The overall safety profile of CT-P42 in DME patients was generally similar to that of EU-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.

Overview of TEAEs by Demographic Subgroup in Study CT-P42 3.1 in DME Patients (Safety Set for Main Study Period)

	Age: < 65		**Age: ≥ 65**	
	CT-P42 (N=101)	**EU-Eylea (N=95)**	**CT-P42 (N=73)**	**EU-Eylea (N=79)**
Total number of TEAEs, n	148	152	121	166
Number of patients with ≥ 1 TEAE, n (%)	65 (64.4%)	62 (65.3%)	44 (60.3%)	55 (69.6%)
Related TEAE	5 (5.0%)	2 (2.1%)	3 (4.1%)	4 (5.1%)
Grade 3 or higher TEAE	20 (19.8%)	19 (20.0%)	20 (27.4%)	22 (27.8%)
TESAE	10 (9.9%)	7 (7.4%)	9 (12.3%)	10 (12.7%)
TEAE leading to study drug discontinuation	3 (3.0%)	3 (3.2%)	3 (4.1%)	3 (3.8%)
	Asian		**White**	
	CT-P42 (N=62)	**EU-Eylea (N=62)**	**CT-P42 (N=112)**	**EU-Eylea (N=112)**
Total number of TEAEs, n	70	75	199	243
Number of patients with ≥ 1 TEAE, n (%)	33 (53.2%)	40 (64.5%)	76 (67.9%)	77 (68.8%)
Related TEAE	5 (8.1%)	1 (1.6%)	3 (2.7%)	5 (4.5%)
Grade 3 or higher TEAE	10 (16.1%)	11 (17.7%)	30 (26.8%)	30 (26.8%)
TESAE	4 (6.5%)	3 (4.8%)	15 (13.4%)	14 (12.5%)
TEAE leading to study drug discontinuation	3 (4.8%)	1 (1.6%)	3 (2.7%)	5 (4.5%)
	Male		**Female**	
	CT-P42 (N=107)	**EU-Eylea (N=96)**	**CT-P42 (N=67)**	**EU-Eylea (N=78)**
Total number of TEAEs, n	153	200	116	118
Number of patients with ≥ 1 TEAE, n (%)	66 (61.7%)	67 (69.8%)	43 (64.2%)	50 (64.1%)
Related TEAE	4 (3.7%)	4 (4.2%)	4 (6.0%)	2 (2.6%)
Grade 3 or higher TEAE	27 (25.2%)	19 (19.8%)	13 (19.4%)	22 (28.2%)
TESAE	13 (12.1%)	10 (10.4%)	6 (9.0%)	7 (9.0%)
TEAE leading to study drug discontinuation	3 (2.8%)	4 (4.2%)	3 (4.5%)	2 (2.6%)

Source: Section 5.3.5.3 Post-hoc Tables 4.08, 4.09, 4.10
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.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity or Tumor Development

Not applicable.

7.6.2 Human Reproduction and Pregnancy

This product was not studied in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

This application included the November 11, 2022, agreed iPSP for the AMD, RVO, DME, and DR indications, (b) (4) submitted to the Agency on February 24, 2023. The Pediatric Review Committee (PeRC) discussed this application on June 19, 2022. The labeling for US- licensed Eylea does not contain pediatric information for the indications for which the Applicant is seeking licensure (AMD, RVO, DME, and DR), and PREA requirements were waived for, or inapplicable to, US-Eylea for those indications. Accordingly, the Agency has determined that no pediatric studies will be required under PREA for this BLA. See QA.I.16, FDA Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Rev. 2) (Sept. 2021).

(b) (4) at this time, the Applicant has fully addressed PREA and no additional pediatric studies are required.

7.5. Safety in the Postmarket Setting

CT-P42 has not yet been marketed.

8. Integrated Assessment of Safety

There is no integrated assessment of safety across trials as the application includes only a single pivotal study (CT-P42 3.1) to support the safety assessment of CT-P42. Study CT-P42 3.1 demonstrated that CT-P42 and Eylea have comparable safety profiles including the change in best corrected visual acuity from baseline to Week 8. Safety was assessed in 175 subjects treated with intravitreal injections of CT-P42 over 52 weeks. Treatment with CT-P42 is considered safe with an adverse event profile similar to Eylea. The adverse events seen were consistent with those seen with most intravitreally administered ophthalmic drugs.

9. Advisory Committee Meeting and Other External Consultations

There were no issues of raised in the review of this application that were thought to benefit from discussion at an Advisory Committee Meeting.

10. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable. Risk Evaluation and Mitigation Strategies are not required for this product.

11. Postmarketing Requirements and Commitments

Not applicable. There are no Postmarketing Requirements or Postmarketing Commitments are not required for this product.

12. Financial Disclosure

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, CELLTRION requested statements of financial interests from a total of 83 principal investigators and 395 sub-investigators for the following study:

Study	Number of Principal Investigators	Number of Sub-Investigators	Total
CT-P42 3.1	83	395	478

As of June 30th, 2023, a total of 478 financial disclosures for the investigators who participated in this trial was received. All principal or sub-investigators returned the financial disclosure information.

Reviewer's Comment: *The applicant did not submit Form 3455 because no investigators reported a disclosable financial interest.*

Covered Clinical Study (Name and/or Number): CT-P42

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 478		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13. Labeling Recommendations

On June 14, 2024, the Division communicated proposed draft labeling to the applicant. The electronic communication with Celltrion was archived in DARRTS for reference.

14. Regulatory Action

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761377 for EYDENZELT (aflibercept-boav) manufactured by Celltrion Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture

of EYDENZELT is well-controlled and will lead to a product that is pure and potent. The comparative analytical data support a demonstration that EYDENZELT is highly similar to US-licensed aflibercept.

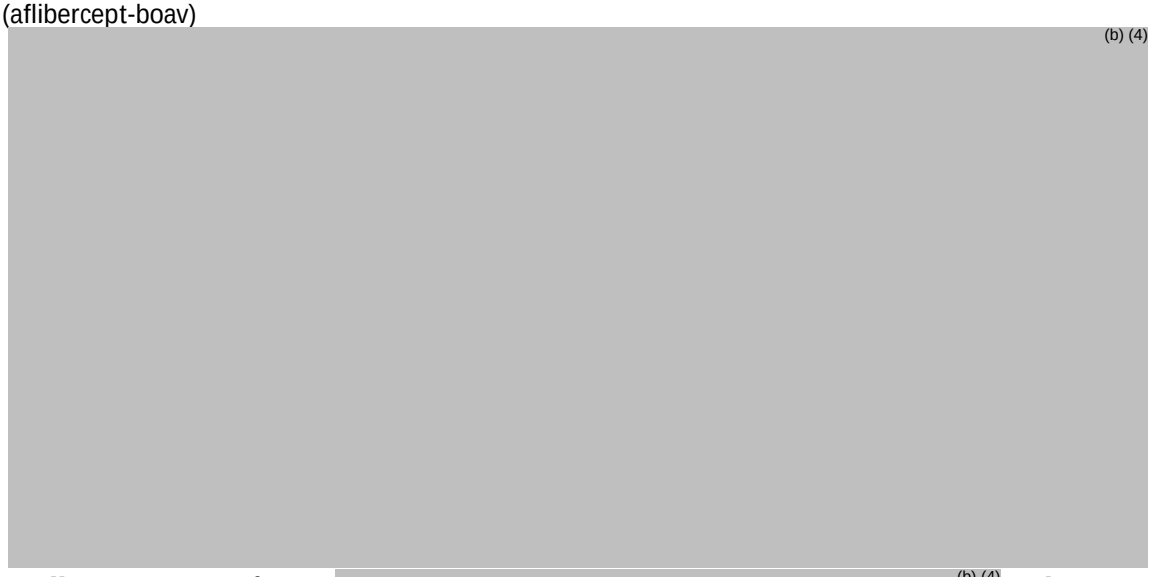
From a CMC standpoint, OPQ is recommending a **Complete Response** letter be issued to CELLTRION, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

The following Complete Response comments should be included in the Action Letter:

Microbiology

1. (b) (4)
2.
3.

4. (b) (4)



5. Following review of DMF (b) (4) and cross- referenced in this application, FDA conveyed deficiencies to the DMF holder. The holder should update the DMF with satisfactory responses to these deficiencies prior to your complete response to your application. Your complete response should include the date(s) of the DMF amendment. The assessment of application approvability and the resolution of DMF deficiencies would be evaluated upon receipt of the complete response. Please work with the DMF holder in resolving the related deficiencies.

Facility Inspection

4. During a recent CGMP inspection and a pre-license inspection (PLI) of Celltrion Inc. (Plant (b) (4) FEI 3005241015), the drug substance manufacturer for this application, our field investigators conveyed deficiencies to the representative of the respective facilities. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Our determination that the facility's responses are satisfactory will depend on a finding that the facility has come into compliance with CGMP and has addressed any deficiencies specific to your application. You should coordinate with the facility for timely resolution of all inspection deficiencies, as well as to determine if any deficiencies may require updates to your application. Your complete response should include the date(s) of the facility's responses(s) to the FDA Form 483. Please refer to the Compliance Program CP 7356.002 for guidance on post-inspection activities specific to GMP compliance evaluation. FDA may determine that a CGMP reinspection and/or additional PLI is needed to confirm satisfactory resolution of inspection deficiencies before this application can be approved. If both CGMP and PLI reinspection are needed, the PLI coverage will generally occur following a determination that the facility is in compliance with CGMP.
5. Following pre-license inspection of (b) (4) , the pre-filled syringe drug product manufacturer listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of

the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

6. Inspection of the (b) (4) is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RHEA A LLOYD
06/27/2024 09:05:09 AM

WILLIAM M BOYD
06/27/2024 09:07:53 AM