

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761377Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Cross-Discipline Team Leader Review

Date	<i>Electronic Stamp Date</i>
From	Rhea Lloyd, MD, Cross Discipline Team Leader William Boyd, MD, Deputy Division Director
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Application Type	351(k) BLA
NDA/BLA #	BLA 761377 IND (b) (4)
Applicant	Celltrion, Inc.
Date of Submission	April 18, 2025
BsUFA Goal Date	October 18, 2025
Proprietary Name	Eydenzelt
Code Name	CT-P42
Nonproprietary Name	aflibercept-boav
Dosage Form, Strength, and Presentation	<ul style="list-style-type: none"> For intravitreal injections: single-dose 2 mg (0.05 mL of 40 mg/mL) glass vial kit For intravitreal injection: single-dose 2 mg (0.05 mL of 40 mg/mL) in a prefilled syringe
Proposed Indication(s)/Population(s)	<p>Same indications as those approved for US-licensed Eylea:</p> <ul style="list-style-type: none"> Neovascular (Wet) Age-Related Macular Degeneration (AMD) Macular Edema Following Retinal Vein Occlusion (RVO) Diabetic Macular Edema (DME) Diabetic Retinopathy (DR)
Proposed Dosing Regimens	<p>Same regimen approved for US-licensed Eylea: Neovascular (Wet) Age-Related Macular Degeneration (AMD)</p> <ul style="list-style-type: none"> The recommended dose for EYDENZELT is 2 mg (0.05 ml of 40 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL of 40 mg/mL solution) via intravitreal injection once every 8 weeks (2 months). Although EYDENZELT 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 aflibercept 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. <p>Macular Edema Following Retinal Vein Occlusion (RVO)</p>

	<ul style="list-style-type: none"> • The recommended dose for EYDENZELT is 2 mg (0.05 mL of 40 mg/mL solution) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). <p>Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)</p> <ul style="list-style-type: none"> • The recommended dose for EYDENZELT is 2 mg (0.05 mL of 40 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL of 40 mg/mL solution) via intravitreal injection once every 8 weeks (2 months). • Although EYDENZELT 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 aflibercept 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).
<p>Recommendation on Regulatory Action</p>	<p>APPROVAL of CT-P42, injection, for intravitreal use as biosimilar to US-Eylea (aflibercept) for the products described below:</p> <ul style="list-style-type: none"> • 2 mg (0.05 mL of 40 mg/mL) in a single-dose vial kit (vial kit) and single-dose prefilled syringe (PFS) as biosimilar to US-Eylea 2 mg (0.05 mL of 40 mg/mL) in a vial kit and PFS. <p style="text-align: right;">(b) (4)</p>

Reviewers of Biosimilar Application

BLA 76137 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, Anh-Thy Ly
OTBB Clinical Reviewer	Milalynn Victorino/ Michelle Luo

BLA 761377 Class 2 Resubmission
 Eydenzelt (CT-P42, aflibercept-boav)
 Cross Discipline Team Leader / Dep. Director Review

OTBB Regulatory Counsel	Laurel Goldberg
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	Abiola Olagundoye-Alawode
DMEPA Team Lead / Reviewer	Valerie Vaughn / Sofanit Getahum
OSI CSO	Roy Blay
Deputy Division Director	William Boyd

1. Background

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

The clinical development of CT-P42 has demonstrated that CT-P42 has no meaningful difference to EU-approved Eylea (EU-Eylea) with regard to efficacy, safety, pharmacokinetics (PK) and immunogenicity in the treatment of subjects with diabetic macular edema (DME). To justify the relevance of the comparative clinical data generated using EU-Eylea to support the assessment of biosimilarity, Celltrion performed a comparative analytical assessment that included three pairwise comparisons between CT-P42, US- Eylea and EU- Eylea to support that CT-P42 is highly similar to US-Eylea and establish a scientific bridge between CT-P42, US-Eylea and EU-Eylea.

Celltrion is seeking licensure of CT-P42 for the following:

- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) strength in a single-use vial kit, for intravitreal use as a proposed (b) (4) biosimilar to U.S.-Eylea 2 mg (0.05 mL of 40 mg/mL) injection in a vial kit and single-dose pre-filled syringe (PFS) for intravitreal use,
- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) in a PFS, for intravitreal use as a proposed (b) (4) biosimilar to U.S.- Eylea 2 mg (0.05 mL of 40 mg/mL) injection in a PFS, for intravitreal use, and
- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) in a PFS, for intravitreal use as a proposed biosimilar to U.S.-Eylea 2 mg (0.05 mL of 40 mg/mL) injection in a vial kit, for intravitreal use.

A 2 mg (0.05 mL of 40 mg/mL) dose of CT-P42 is for the following indications which 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)

On June 27, 2024, a Complete Response (CR) letter issued due to multiple deficiencies including product quality, microbiology and facility inspections issues. A BPD Type 1 meeting was conducted on August 26, 2024, to discuss Celltrion’s proposed plan to resolve deficiencies in the CR letter. Following implementation of the proposed plan, on September 26, 2024, Celltrion submitted a Class 2 Resubmission stating that all of the deficiencies listed in the CR

letter had been addressed. On March 26, 2025, a CR letter was issued again for the remaining unsolved manufacture facility inspection issues.

On April 18, 2025, this Class 2 Resubmission of the BLA was submitted by Celltrion. The Office of Pharmaceutical Quality (OPQ), CDER has completed assessment 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 CTP42 is highly similar to US-licensed Eylea, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

2. Product Quality

From The Office of Pharmaceutical Quality (OPQ), Resubmission Executive Summary Review Number 3 finalized in DARRTS on 8/21/2025:

1. Application/Product Information

BLA number	761377 (Seq. 0047)
Submission Type	Class II Resubmission: Second Complete Response Resubmission
Regulatory Pathway	351(k) Biologics License Application Proposed biosimilar [REDACTED] ^{(b) (4)} product to US-licensed Eylea (aflibercept)
Associated IND/BLA	PIND 147335 Refer to meeting minutes dated June 22, 2020, August 30, 2021, August 15, 2022, and August 31, 2023, and August 26, 2024, for BPD Type 1, 2 and 4 meetings between the applicant and the Agency.
Review Designation	Standard Complete Response Resubmission (Second resubmission)
Applicant	CELLTRION, Inc.
Indication	Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)

Rx/OTC dispensed	Rx		
Drug Product Name	Proprietary Name: EYDENZELT		
	Non-proprietary Name: aflibercept-boav		
	Code name: CT-P42		
Drug Product Name	OBP Naming: FUS: MABFRAG HUMAN (IGG1); RPROTFRAG P35968 (VGFR2_HUMAN); RPROTFRAG P17948 (VGFR1_HUMAN) [CT-P42]		
Drug Product Description	CT-P42 is a recombinant fusion protein produced in a Chinese Hamster Ovary (CHO) cell line and consists of portions of the human vascular endothelial growth factor (VEGF) receptors 1 and 2 (VEGFR-1 and VEGFR-2) extracellular domains fused to the Fc portion of human IgG1. CT-P42 drug product is a sterile, Preservative-free solution that is presented as a single-use vial and a pre-filled syringe (PFS). Each vial and PFS contains 2 mg of CT-P42, 0.038 mg (b) (4) Histidine, 0.033 mg L-Histidine monohydrochloride monohydrate, 0.038 mg Sodium chloride, 5 mg trehalose, and 0.015 mg Polysorbate 20 at a pH 6.2.		
Dosage Form	Injection (solution)		
Strength	2 mg/0.05 mL (40 mg/mL)		
Route of Administration	Intravitreal injection		
Primary Container Closure System	Vial: Glass vial (2 (b) (4) vial, type (b) (4) clear glass), stopper (13 mm, (b) (4) rubber), and cap (13 mm, aluminum seal with a (b) (4)) PFS: 0.5 mL (b) (4) syringes with (b) (4) rubber plunger stoppers and (b) (4) rubber luer lock tip caps with (b) (4).		
Co-packaged Product Information	A vial kit contains one 18 gauge x 1½ inch sterile filter needle (5 µm), one 1 mL sterile Luer lock plastic syringe, and one 30 gauge x ½ inch sterile injection needle.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Barry Gertz	Samuel Mindaye
	Drug product		

	Facility/Microbiology	Ekaterina Allen	Zhong Li (facility) Maxwell Van Tassell (Microbiology)
	RBPM	Kristine Leahy	
	ATL	Samuel Mindaye	
OPQ Issued Consults	None		

Regulatory history: The original BLA 761377 submission for CT-P42 (aflibercept-boav), proposed (b) (4) biosimilar to US-licensed Eylea received a Complete Response (CR) recommendation on June 27, 2024, due to deficiencies that included product quality, microbiology, and facility deficiencies (at Celltrion, Inc., Korea DS manufacturing, and at (b) (4), for PFS DP manufacturing). To address deficiencies identified during pre-license inspection (PLI), Celltrion transferred the manufacture of unassembled PFS DP from (b) (4) to Patheon Italia S.p.A. Ferentino, Italy (FEI 3004110157) and the assembly process was transferred from (b) (4) to Steripack Medical, Poland. Based on these changes, a complete response to the Agency’s CR letter was re- submitted on September 26, 2024 (seq. 0038). The information and data provided in seq. 0038 and subsequent amendments were reviewed and the manufacturing sites (DS at Celltrion, Inc., Korea, and PFS DP at Patheon Italia S.p.A. Ferentino, Italy) were inspected. While the PLI of the DS site (Celltrion, Inc., Korea) confirmed compliance, the status of the DP facility at Thermo Fisher Scientific (Patheon Italia S.p.A.), Ferentino, Italy (FEI: 3004110157) concluded with a withhold recommendation. The ATL for the first round CR resubmission is provided in DARRTS (uploaded on March 25, 2025).

Therefore, the first CR resubmission received another CRL on March 26, 2025. Then, Celltrion along with Thermo Fisher Scientific (Patheon Italia S.p.A.) resolved the deficiencies described in the Post-Application Action Letter (PAAL, from March 28th, 2025), and resubmitted BLA 761377 CR for the second time on April 18, 2025 (S/N0047). This executive summary covers the product quality review of the second round CR resubmission.

a. Recommendation and Conclusion on Approvability

Recommendation: Approval

The Office of Pharmaceutical Quality (OPQ), CDER has completed assessment 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 CTP42 is highly similar to US-licensed Eylea (aflibercept), notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. CMC Information for Action Letter

• **Manufacturing Location:**

• **Drug Substance:**

Celltrion Inc. (Plant^(b)₍₄₎), (FEI 3005241015)
^(b)₍₄₎ Academy-ro, Yeonsu-gu,
Incheon, 22014, Republic of Korea

• **Drug Product:**

PFS: Patheon Italia S.p.A. (FEI 3004110157)

Via Morolense 5,
Ferentino, 03013, Italy

Vial: Patheon Italia SpA, (FEI# 3003065803)

Viale Gian Battista Stucchi 110,
Monza, 20900, Italy

c. Fill size and dosage form: 2 mg/0.05 mL (40 mg/mL), injection

d. Dating Period:

• **Drug Product:**

Vial: 36 months when stored at $5 \pm 3^{\circ}\text{C}$.

PFS: 24 months when stored at $5 \pm 3^{\circ}\text{C}$.

• **Drug Substance:** ^(b)₍₄₎ months when stored at ^(b)₍₄₎ °C.

• **Vial kit components**

- 1½ inch 5 µm sterile filter needle
- 1 mL sterile Luer lock syringe
- ½ inch sterile injection needle

• **Stability Option:**

For stability protocols:

- Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process performance qualification lots.
- We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

• **Exempt from lot release:** Yes, CT-P42 is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments (PMCs), Requirements, Agreements, and/or Risk Management Steps, as applicable: None

4. Basis for Recommendation

a. Summary:

BLA 761377 was originally submitted on June 29, 2023 for CT-P42 (aflibercept-boav). CT-P42 was proposed as a ^(b)₍₄₎ biosimilar to US-licensed Eylea for the same strength, dosage form, indications, and route of administration as for the 2 mg/0.05 mL (40 mg/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. For FDA's review of the information provided in BLA 761377 (original submission and successive resubmission), refer to the assessment of the product quality including the comparative analytical assessment in the following database.

- **Original BLA:** product quality primary: BLA 761377 Review Memo 04092024.PDF, Microbiology and facility: **DS:** B761377 DS Micro Review-OPMA and **DP:** BLA_761377_Celltrion_Final_DP-OPMA),
 - **First cycle resubmission:** product quality BLA STN 761377 Resubmission Review and Microbiology and facility Resub-BLA761377-OPMA-Micro-and-Facility
 - **Second cycle resubmission:** microbiology and facility reviews BLA761377-resub-47_Celltrion_DP-1
- f. **ATL Executive Summary provided in DARRTS:** Original BLA on June 20, 2024 and first cycle resubmission March 25, 2025.

The ATL memorandum and memorandum addendum in the above references detail the bases for the subdiscipline approval recommendations except for the overall compliance status of the manufacturing facilities. This memorandum addresses the CR issues related to deficiencies identified at the previous inspections of the DP manufacturing and testing facility at Thermo Fisher Scientific (Patheon Italia S.p.A.), Ferentino, Italy (FEI: 3004110157).

In S/N0047 received on April 18, 2025, Celltrion resubmitted BLA761377 (complete response to the second CRL). The second CR resubmission references additional information provided to the Agency including by Thermo Fisher Scientific (Patheon Italia S.p.A.) submitted on 03/11/2025 responding to items in the initial Form 483, follow-up status update submitted on 03/21/2025, response to post-action letter submitted on 04/07/2025, and further status updates submitted on 04/24/2025 and 05/08/2025. The compliance reviewer evaluated all the responses and additional information and concluded that deficiencies identified during the PLI of Patheon Italia S.p.A. Ferentino, Italy (FEI 3004110157) have been adequately addressed and the facility became compliant. Therefore, approval of the facility was recommended.

Summary of the status of establishments cited in BLA761377 is provided in the table below.

In addition, Celltrion submitted results of a (b) (4) study to address the non-approvability comment included in the CRL (from March 26, 2025). The OPMA assessor found the non-approvability deficiency addressed adequately.

Taken together, the Applicant has adequately addressed all the deficiencies including PLI items identified in the previous CRLs for BLA 761377. Therefore, the OPQ recommends approval of this application.

Summary of Establishment Information

Facility name and address	FEI	Responsibilities and profile code(s)	Status
CELLTRION Inc. (b) (4) Academy-ro, Yeonsu-gu, Incheon, N/A, Republic of Korea, 22014	3005241015	Production of CT-P42 drug substance, Release testing of CT-P42 drug substance, Stability testing of CT-P42 drug substance, Storage of the MCB and WCB, Testing of CT-P42 unprocessed bulk, Release testing of CT-P42 drug product, Stability testing of CT-P42 drug product	Approve - Based on Waiver granted by OPMA/OBP

BLA 761377 Class 2 Resubmission
 Eydenzelt (CT-P42, aflibercept-boav)
 Cross Discipline Team Leader / Dep. Director Review

Facility name and address	FEI	Responsibilities and profile code(s)	Status
CELLTRION Inc. (b) (4) Academy-ro, 51 beon-gil, Yeonsu gu, Incheon, N/A, Republic of Korea, 22014	3005241015	Release of CT-P42 drug substance, Release testing of CT- P42 drug substance, Stability testing of CT-P42 drug substance, Testing of CT-P42 unprocessed bulk, Storage of the MCB and WCB, Release testing of CT-P42 drug product, Stability testing of CT-P42 drug product, Release of CT-P42 drug product, Holding and storing of CT-P42 drug product	Approve - Based on Waiver granted by OPMA/OBP
BioReliance Ltd. Todd Campus, West of Scotland Science Park, Glasgow, Lanarkshire, Scotland, G20 0XA	3005343934	Production of (b) (4)	No Evaluation Necessary
BioReliance Ltd. Innovation Park, Hillfoots Road, Stirling, N/A, Scotland, FK9 4NF	3005619549	Storage of (b) (4)	No Evaluation Necessary
BioReliance Ltd Pentlands Science Park, Penicuik, N/A, Scotland, EH26 0PZ	3005619544	Testing of the (b) (4)	No Evaluation Necessary
WuXi Advanced Therapies, Inc, 400 Rouse Blvd, Philadelphia, PA 19112- 1904, USA	(b) (4)	Testing of CT-P42 (b) (4)	Approve - Based on Previous History
Samsung Biologics Co., Ltd.300, Songdo bio-daero, Yeonsu-gu, Incheon, N/A, Republic of Korea, 21987	3010479596	Testing of CT-P42 (b) (4)	Approve - Based on Previous History
Patheon Italia S.p.A. Viale Gian Battista Stucchi 110 , Monza, N/A, Italy, 20900	3003065803	Production of CT-P42 drug product, release testing (Endotoxin, Sterility), Holding and storing of CT-P42 drug product	Approve - Based on Waiver granted by OPMA/OBP
STERIPACK MEDICAL POLAND SP Z O O UI. Japonska 1, Jelcz-Laskowice, Dolnoslaskie, N/A, Poland, 55-220	3007766601	Vial: Secondary packaging (labelling and cartoning) PFS: Secondary packaging (labelling, assembly, blistering and cartoning); (b) (4) packaging, Holding and storing of CT-P42 aDP and fDP, stability testing of (b) (4) CT-P42 DP	Approve - Based on Previous History
CELLTRION Pharm, Inc. 82, 2 Sandan-ro, Ochang- eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea, 28117	3012279978	Vial: Secondary packaging (labelling and cartoning) PFS: Secondary packaging (cartoning)	Approve - Based on Previous History
Patheon Italia S.p.A. Via Morolense 5, , Ferentino, N/A, Italy, 3013	3004110157	Production of CT-P42 drug product (uDP), Primary packaging and storage, Release testing of CT-P42 uDP	Approve - Based on Waiver granted by OPMA/OBP
Sterigenics Belgium Petit Rechain SA, Avenue André Ernst 21, B-4800 Petit- Rechain (Verviers), Belgium	3002807111	(b) (4)	Approve - Based on Waiver granted by OPMA/OBP
Sterigenics Germany GmbH Kasteler Str. 45, Wiesbaden, N/A, Germany, 65203	3006003617	Release (sterility of syringe) testing of (b) (4) CT-P42 product	Approve - Based on Previous History

a. Subdiscipline Recommendation:
Drug Substance - Adequate


Drug Product	-	Adequate
Immunogenicity Assays	-	Adequate
CAA	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

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

c. 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.

d. Life-Cycle Considerations

- Established Conditions based on ICH Q12 principles: No
- 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.

e. Drug Product:

- Protocols approved:
 - Post-approval annual stability protocol and stability protocol for the extension of drug product shelf-life
- Residual risk: None
- Future inspection points to consider: none

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

3. Nonclinical Pharmacology/Toxicology

No relevant nonclinical studies were performed during the clinical development of CT-P42.

4. Clinical Pharmacology

The Clinical Pharmacology review finalized March 18, 2024, recommended approval. No new clinical pharmacology information was submitted in this resubmission.

5. Clinical Microbiology

Not applicable. This product is not an anti-infective.

6. Clinical Efficacy /Safety

The clinical review finalized on June 27, 2024, recommended approval.

Study CT-P42 3.1 is a comparative clinical study to assess the efficacy, safety, PK and immunogenicity of CT-P42 and EU-Eylea in the treatment of patients with diabetic macular edema (DME). The study met its primary efficacy endpoint, the Mean Change from Baseline in BCVA at Week 8 by Treatment. The 90% confidence interval (CI) for the estimate of treatment difference in LS means in the Per Protocol (PP) set fell within the equivalence margin of ± 3 letters (90% CI: [-0.70, 1.45] for PP set). This finding was confirmed in the Full Analysis Set (FAS) (90% CI: [-0.52, 1.67] for FAS set). 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). This study demonstrated that there are no meaningful differences between CT-P42 and EU-Eylea.

The submitted comparative clinical study (CT-P42 3.1) supports the safety assessment of CT-P42. Study CT-P42 3.1 demonstrated that CT-P42 and EU-Eylea have comparable safety profiles including the change in best corrected visual acuity from baseline to Week 8, safety and immunogenicity. Safety was assessed in 174 subjects treated with intravitreal injections of CT-P42 over 52 weeks. Intravitreal injections were performed using the vial kit presentation. During the 4-week Extension Study Period, the pre-filled syringe presentation was used for intravitreal injections. Treatment with CT-P42 is considered safe with an adverse event profile similar to EU-Eylea. The adverse events seen were consistent with those seen with most intravitreally administered ophthalmic drugs. Overall, the comparative safety data support a demonstration that there are no meaningful differences between CT-P42 and EU-Eylea.

CT-P42 was approved in South Korea on May 29, 2024, and is currently under regulatory review in several regions – the United States, Europe & European Economic Area, ^{(b) (4)} Australia and ^{(b) (4)}.

As of July 31, 2024, CT-P42 has not been marketed in any regions and there is no post-marketing data available to report.

7. DMEPA / OPDP

Labeling consultants, including Division of Medication Error Prevention and Analysis 1 (DMEPA1) and the Office of Prescription Drug Promotion (OPDP) reviewed the proposed labeling. In the Division of Medication Error Prevention and Analysis 1 (DMEPA1) review finalized on 9/16/25, DMEPA1 concluded that [their] re-assessment did not identify any names that represent a potential source of drug name confusion. Therefore, we maintain that the proposed proprietary name, Eydenzelt, is conditionally acceptable.

From the DMEPA1 review finalized on July 29, 2025:

CONCLUSION

Our evaluation of the proposed Eydenzelt Prescribing Information (PI), Prefilled Syringe (PFS) and Vial container labels, PFS blister and carton labeling did not identify additional areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDIX A. LABELS AND LABELING

List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^g along with postmarket medication error data, we reviewed the following Eydenzelt labels and labeling submitted by Celltrion, Inc..

- Prescribing Information received on April 18, 2025, available from:
 - Annotated version: <\\CDSESUB1\EVSPROD\bla761377\0047\m1\us\draft-labeling-text-tracked.docx>
 - Clean version: <\\CDSESUB1\EVSPROD\bla761377\0047\m1\us\draft-labeling-text.docx>
- PFS and Vial container labels received on April 18, 2025
- PFS blister and carton labeling received on April 18, 2025

8. Advisory Committee Meeting

No Advisory Committee was necessary or planned for this supplement.

9. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients 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.

The labeling for US- 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 for those indications. (b) (4)

Refer to Pediatric section in BMER dated on 6/27/2024 in DARRTS. There is no new pediatric information submitted for this resubmission. At this time, no pediatric studies are required under PREA for this BLA.

10. Other Relevant Regulatory Issues

None.

11. Labeling

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The Office of Prescription Drug Promotion (OPDP) completed review of the proposed Prescribing Information (PI), container labels, and carton labeling on February 25, 2025.

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) completed review of the carton labeling and container labels on April 18, 2025, and found the revisions to be acceptable.

The Office of Product Quality Assessment III (OPQA-III) completed a final review on August 18, 2025, and found the PI, container labels, and carton labeling to be acceptable.

BLA 761377 Class 2 Resubmission
Eydenzelt (CT-P42, aflibercept-boav)
Cross Discipline Team Leader / Dep. Director Review

Following is the agreed PI and the agreed container labels and carton labeling submitted on April 18, 2025.

41 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

12. Recommendations

In considering the totality of the evidence submitted, FDA has determined that the Applicant has provided adequate data and information to support a demonstration that CT-P42 is highly similar to U.S.-Eylea, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P42 and U.S.-Eylea. The data and information provided by the Applicant are sufficient to demonstrate that CT-P42 can be expected to produce the same clinical results as those of U.S.-Eylea in any given patient.

(b) (4)
Therefore, the data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that:

- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) for intravitreal use in a single-use vial kit meets the applicable requirements for licensure as (b) (4) U.S.-Eylea 2 mg (0.05 mL of 40 mg/mL) for intravitreal use in a vial kit and single-dose pre-filled syringe (PFS), and
- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) for intravitreal use in a PFS meets the applicable requirements for licensure as (b) (4) U.S.-Eylea 2 mg (0.05 mL of 40 mg/mL) for intravitreal use in single-dose PFS,

for the following indication for which US-Eylea has been previously approved and for which the Applicant is seeking licensure of CT-P42:

- Neovascular (wet) age-related macular degeneration (AMD).
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

Healthcare providers administer US-Eylea to all patient populations using either a vial kit or PFS. CT-P42's vial kit may be licensed for use as (b) (4) with either the US-Eylea vial kit or PFS given that the difference between a vial kit and a PFS would not be expected to result in any clinically meaningful difference in this case, as healthcare providers can be expected to manage risks associated with administering to patients using a vial kit or a PFS in accordance with the administration instructions in the labeling. Thus, the Applicant does not need to provide additional data or information to justify licensing the CT-P42 vial kit for use as (b) (4) with the US-Eylea PFS under these specific circumstances.¹

The review team recommends (b) (4) that:

¹ See FN 2 *supra*.

- [Redacted] (b) (4)
- [Redacted]

The review team also recommends an Approval for CT-P42, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS as biosimilar to US-Eylea 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS.

[Redacted] (b) (4)

[Redacted] (b) (4)

This BLA has been administratively split so that the Approval of CT-P42, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS as biosimilar to US-Eylea 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS will remain in BLA 761377/Original 1. BLA 761377/Original 1 will receive an Approval letter.

[Redacted] (b) (4)

[Redacted] (b) (4)

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
10/02/2025 09:54:16 AM

WILLIAM M BOYD
10/02/2025 10:29:25 AM

Cross-Discipline Team Leader Review

Date	<i>Electronic Stamp Date</i>
From	Rhea Lloyd, MD, Cross Discipline Team Leader William Boyd, MD, Deputy Division Director
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Application Type	351(k) BLA
NDA/BLA #	BLA 761377 IND (b) (4)
Applicant	Celltrion, Inc.
Date of Submission	September 26, 2024
BsUFA Goal Date	March 26, 2025
Proprietary Name	Eydenzelt
Code Name	CT-P42
Nonproprietary Name	aflibercept-boav
Dosage Form, Strength, and Presentation	<ul style="list-style-type: none"> For intravitreal injections: single-dose 2 mg (0.05 mL of 40 mg/mL) glass vial For intravitreal injection: single-dose 2 mg (0.05 mL of 40 mg/mL) in a prefilled syringe
Proposed Indication(s)/Population(s)	<p>Same indications as those approved for US-licensed Eylea:</p> <ul style="list-style-type: none"> Neovascular (Wet) Age-Related Macular Degeneration Macular Edema Following Retinal Vein Occlusion Diabetic macular edema Diabetic retinopathy
Proposed Dosing Regimens	<p>Same regimen approved for US-licensed Eylea:</p> <p>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</p> <ul style="list-style-type: none"> 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. <p>Macular Edema Following Retinal Vein Occlusion (RVO)</p> <ul style="list-style-type: none"> The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly).

	<p>Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)</p> <ul style="list-style-type: none"> • 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 76137 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
OTBB Regulatory Counsel	Laurel Goldberg
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
Office Director	Charles Ganley

1. Background

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

The clinical development of CT-P42 has demonstrated that CT-P42 is similar to EU-approved Eylea (EU-Eylea) with regard to efficacy, safety, pharmacokinetics (PK) and immunogenicity in the treatment of subjects with diabetic macular edema (DME). To justify the relevance of the comparative clinical data generated using EU-Eylea to support the assessment of biosimilarity, Celltrion performed a comparative analytical assessment that included three pairwise comparisons between CT-P42, US- Eylea and EU- Eylea to support that CT-P42 is highly similar to US-Eylea and establish a scientific bridge between CT-P42, US-Eylea and EU-Eylea.

Celltrion is seeking licensure of CT-P42 for the following:

- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) strength in a single-use vial kit, for intravitreal use as a proposed (b) (4) biosimilar to U.S.-Eylea 2 mg (0.05 mL of 40 mg/mL) injection in a vial kit and single-dose pre-filled syringe (PFS) for intravitreal use,
- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) in a PFS, for intravitreal use as a proposed (b) (4) biosimilar to U.S.- Eylea 2 mg (0.05 mL of 40 mg/mL) injection in a PFS, for intravitreal use, and
- CT-P42 injection, 2 mg (0.05 mL of 40 mg/mL) in a PFS, for intravitreal use as a proposed biosimilar to U.S.-Eylea 2 mg (0.05 mL of 40 mg/mL) injection in a vial kit, for intravitreal use.

A 2 mg (0.05 mL of 40 mg/mL) dose of CT-P42 is for the following indications which 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)

On June 27, 2024, a Complete Response (CR) letter issued due to multiple deficiencies including product quality, microbiology and facility inspections issues. A BPD Type 1 meeting was conducted on August 26, 2024, to discuss on Celltrion’s proposed plan to resolve deficiencies in the CR letter. Following implementation of the proposed plan, on September 26, 2024, Celltrion submitted a Class 2 Resubmission stating that all of the deficiencies listed

in the CR letter had been addressed.

2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER has completed assessment of resubmission of BLA 761377 for CT-P42 manufactured by Celltrion, Inc. The data submitted in this application are inadequate to support the conclusion that the manufacture of CT-P42 is well-controlled and leads to a product that is pure and potent. However, the comparative analytical data support a demonstration that CTP42 is highly similar to US-Eylea, notwithstanding minor differences in clinically inactive components.

Overall, from a CMC standpoint, OPQ is recommending a **Complete Response letter be issued to Celltrion, Inc.** to outline the deficiencies noted in Section 12 below and the information and data that will be required to support approval. Please refer to the Office of Biotechnology Products (OBP) Executive Summary review finalized on March 25, 2025 in DARRTS.

Per that review:

1. Application/Product Information

BLA number	761377 (Seq. 0038)
Submission Type	Class II Resubmission
Regulatory Pathway	351(k) Biologics License Application Proposed biosimilar [REDACTED] ^{(b) (4)} product to US-licensed Eylea (aflibercept)
Associated IND/BLA	PIND 147335 Refer to meeting minutes dated June 22, 2020, August 30, 2021, August 15, 2022, and August 31, 2023, and August 26, 2024, for BPD Type 1, 2 and 4 meetings between the applicant and the Agency.
Review Designation	Standard review
Applicant	CELLTRION, Inc.

Indication	Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: EYDENZELT (Proposed)
	Non-proprietary Name: aflibercept-xxxx
	Code name: CT-P42
	OBP Naming: FUS: MABFRAG HUMAN (IGG1); RPROTFRAG P35968 (VGFR2_HUMAN); RPROTFRAG P17948 (VGFR1_HUMAN) [CT-P42]
Drug Product Description	CT-P42 is a recombinant fusion protein produced in a Chinese Hamster Ovary (CHO) cell line and consists of portions of the human vascular endothelial growth factor (VEGF) receptors 1 and 2 (VEGFR-1 and VEGFR-2) extracellular domains fused to the Fc portion of human IgG1. CT-P42 drug product is a sterile, Preservative-free solution that is presented as a single-use vial and a pre-filled syringe (PFS). Each vial and PFS contains 2 mg of CT-P42, 0.038 mg (b) (4) Histidine, 0.033 mg L-Histidine monohydrochloride monohydrate, 0.038 mg Sodium chloride, 5 mg trehalose, and 0.015 mg Polysorbate 20 at a pH 6.2.
Dosage Form	Injection (solution)
Strength	2 mg/0.05 mL (40 mg/mL)
Route of Administration	Intravitreal injection
Primary Container Closure System	Vial: Glass vial (2 (b) (4) vial, type (b) (4) clear glass), stopper (13 mm, (b) (4) rubber), and cap (13 mm, aluminum seal (b) (4)) PFS: 0.5 mL (b) (4) syringes with (b) (4) rubber plunger stoppers and (b) (4) rubber luer lock tip caps with (b) (4).
Co-packaged Product Information	A vial kit contains one 18 gauge x 1½ inch sterile filter needle (5 µm), one 1 mL sterile Luer lock plastic syringe, and one 30 gauge x ½ inch sterile injection needle.

OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Barry Gertz	Samuel Mindaye
	Drug product		
	Facility/Microbiology	Ekaterina Allen	Zhong Li (facility) Maxwell Van Tassell (Microbiology)
	RBPM	Kristine Leahy	
	ATL	Samuel Mindaye	

OPQ Issued Consults	CDRH consult ICCR# 01026470
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Regulatory history: The original BLA 761377 submission for CT-P42 (aflibercept, proposed biosimilar to US-licensed Eylea) received a Complete Response (CR) recommendation (CR letter received on June 27, 2024) due to deficiencies that included product quality, microbiology, and facility deficiencies (at Celltrion, Inc., Korea drug substance manufacturing, and at (b) (4) PFS drug product manufacturing). A BPD Type 1 meeting was conducted on August 26, 2024 to discuss on Celltrion’s proposed plan to resolve product quality deficiencies. Following implementation of the proposed plan, Celltrion re-submitted a complete response to the Agency’s CR letter on September 26, 2024. This executive summary covers the product quality review of the information and data provided in the complete response (seq. 0038) and subsequent amendments. Primary product quality reviews of the resubmission have been uploaded in Panorama ([BLA STN 761377 Resubmission Review](#) for product quality and [Resub-BLA761377-OPMA-Micro-and-Facility](#) for microbiology and facility reviews). In addition, review of the original BLA can be referred from Panorama ([BLA 761377 Review Memo 04092024.PDF](#)).

a. **Recommendation and Conclusion on Approvability Recommendation:**

Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER has completed assessment of BLA 761377 for CT-P42 manufactured by Celltrion, Inc. The data submitted in this application are inadequate to support the conclusion that the manufacture of CT-P42 is well-controlled and leads to a product that is pure and potent. However, the comparative analytical data support a demonstration that CTP42 is highly similar to US- licensed Eylea, notwithstanding minor differences in clinically inactive components. Overall, 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.

b. Draft Complete Response Comments and Additional Comments for Action Letter

The following deficiency should be included in the **Complete Response Letter**.

Facility Inspection

Following a pre-license inspection (PLI) of Thermo Fisher Scientific (Patheon Italia S.p.A.), Ferentino, Italy (FEI: 3004110157) 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. Satisfactory responses from the facility are needed before this application can be approved. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. The assessment of the 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 to resolve the related deficiencies.

Additional: The following deficiency should be included as **not approvability comment**.

[Redacted] (b) (4)

4. Basis for Recommendation

a. Summary:

BLA 761377 was originally submitted on June 29, 2023 for CT-P42 (aflibercept-xxxx). CT-P42 was proposed as [Redacted] (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 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 acts via VEGFR-1 and VEGFR-2 and 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. Assessment of the original BLA including the comparative analytical assessment is provided in Panorama ([BLA 761377 Review Memo 04092024.PDF](#)) and the ATL Executive Summary is provided in DARRTS (June 20, 2024).

The original submission received a Complete Response (CR) recommendation on 27 June 2024 due to deficiencies that included product quality, microbiology, and facility. Specifically, the CR items included:

- [Redacted] (b) (4)

- (b) (4)
- Deficiencies in the information provided in DMF (b) (4) conveyed.
 - Deficiencies in CT-P42 DS manufacturing and testing facility, Celltrion, Inc (FEI# 3005241015), and CT-P42 unassembled drug product (uDP) manufacturing facility, (b) (4).

To resolve these deficiencies, a BPD Type 1 meeting between the applicant and FDA was conducted on August 26, 2024. During the meeting, Celltrion discussed their plan to address all deficiencies listed in the CRL in the upcoming resubmitted BLA. They proposed to transfer the manufacture of unassembled CT-P42 DP from (b) (4) to Patheon Italia S.p.A. Ferentino, Italy (FEI 3004110157). The uDP is further assembled into PFS and packaged into a (b) (4) at (b) (4). Celltrion proposed to transfer the assembly process from (b) (4) to Steripack Medical, Poland. FDA provided feedback about their plan as documented in BPD Type 1 meeting minutes. Celltrion implemented the planned remediation and re-submitted the BLA on 26 September 2024, with a complete response to the CR letter. A limited CMC dossier was submitted targeted to addressing the issues detailed in the CRL and the information is provided in SN0038 and subsequent amendments (SN0040, SN0042, SN0043, SN0044, and SN0045). Microbiology and sterility sections of the complete response (CR items 1- 8 and additional comment) were assessed by the OPMA team, and the review is uploaded in Panorama ([Resub-BLA761377-OPMA-Micro-and-Facility](#)). The new CMC data submitted to support manufacturing process transfer (CR item #7) and validation of the process at the new sites (Patheon for uDP manufacture and Steripack for assembly into PFS) were assessed by the OPQAIII team and the review memo is available in Panorama ([BLA STN 761377 Resubmission Review](#)).

Overall, the CMC data and discussion provided in response to the CR items were adequate. The manufacturing processes have been successfully transferred from (b) (4) to Patheon Italia S.p.A. (for the uDP) and from (b) (4) to Steripack for the assembly. Three consecutive lots were successfully manufactured at-scale, confirming the process transfer did not significantly impact product quality. The technology transfer was supported by comprehensive analytical comparability study as well as process validation at the new sites. Regarding adequacy of the facility, a pre-license inspection (PLI) of Celltrion, Inc., Korea (FEI 3005241015) was conducted from January 6 to January 14, 2025. At the conclusion of the inspection, no Form FDA 483 was issued. In addition, a PLI of Patheon Italia SpA, Italy (FEI 3004110157) was performed from February 10 to February 18, 2025. At the conclusion of the inspection, a 6-item Form FDA 483 was issued, and the initial field recommendation was **“withhold”** due to the objectionable conditions related to quality oversight, (b) (4) practices and inadequate visual inspection program. The recommendation was then upheld during compliance review.

Taken together, even though the totality of comparative analytical assessment data provided in the original BLA support a demonstration that Eydenzelt (aflibercept-xxxx) is highly similar to US-licensed Eylea, notwithstanding minor differences in clinically inactive

components with that of US-licensed Eylea, OPQ is recommending a **Complete Response letter** be issued to Celltrion, Inc. to outline the deficiencies noted above (section 3 of this memo) and the information and data that will be required to support approval.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assays	-	Adequate
CAA	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

3. Nonclinical Pharmacology/Toxicology

No relevant nonclinical studies were performed during the clinical development of CT-P42.

4. Clinical Pharmacology

The Clinical Pharmacology review finalized March 18, 2024, recommended approval. No new clinical pharmacology information was submitted in this resubmission.

5. Clinical Microbiology

Not applicable. This product is not an anti-infective.

6. Clinical Efficacy /Safety

The clinical review finalized on June 27, 2024, recommended approval.

Study CT-P42 3.1 is a comparative clinical study to assess the efficacy, safety, PK and immunogenicity of CT-P42 and EU-Eylea in the treatment of patients with diabetic macular edema (DME). The study met its primary efficacy endpoint, the Mean Change from Baseline

in BCVA at Week 8 by Treatment. The 90% confidence interval (CI) for the estimate of treatment difference in LS means in the Per Protocol (PP) set fell within the equivalence margin of ± 3 letters (90% CI: [-0.70, 1.45] for PP set). This finding was confirmed in the Full Analysis Set (FAS) (90% CI: [-0.52, 1.67] for FAS set). 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). This study demonstrated that there are no meaningful differences between CT-P42 and EU-Eylea. 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).

The submitted comparative clinical study (CT-P42 3.1) supports the safety assessment of CT-P42. Study CT-P42 3.1 demonstrated that CT-P42 and EU-Eylea have comparable safety profiles including the change in best corrected visual acuity from baseline to Week 8, safety and immunogenicity. Safety was assessed in 174 subjects treated with intravitreal injections of CT-P42 over 52 weeks. Intravitreal injections were performed using the vial kit presentation. During the 4-week Extension Study Period, the pre-filled syringe presentation was used for intravitreal injections. Treatment with CT-P42 is considered safe with an adverse event profile similar to EU-Eylea. The adverse events seen were consistent with those seen with most intravitreally administered ophthalmic drugs. Overall, the comparative safety data support a demonstration that there are no meaningful differences between CT-P42 and EU-Eylea.

CT-P42 was approved in South Korea on May 29, 2024, and is currently under regulatory review in several regions – the United States, Europe & European Economic Area, ^{(b) (4)} Australia and ^{(b) (4)}.

As of July 31, 2024, CT-P42 has not been marketed in any regions and there is no post-marketing data available to report.

7. DMEPA / OPDP

Labeling consultants, including Division of Medication Error Prevention and Analysis 1 (DMEPA1) and the Office of Prescription Drug Promotion (OPDP) reviewed the proposed labeling.

From the DMEPA1 review finalized on December 18, 2024:

CONCLUSION

We evaluated the proposed Eydenzelt Prescribing Information (PI) and determined that it is acceptable from a medication error perspective.

However, the proposed Eydenzelt PFS label and PFS blister labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Celltrion, Inc. in Section 4.

RECOMMENDATIONS FOR CELLTRION, INC.

Table 2. Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
PFS Label			
1.	As currently presented, the dosage form “ <i>injection</i> ” is not included on the principal display panel (PDP).	The dosage form is considered to be “critical information” that should appear on the PDP to “ <i>allow for proper identification of the product.</i> ” For more information see Guidance for industry “ <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.c</i> ”	Add the dosage form “ <i>injection</i> ” on the PDP. To ensure sufficient space, we recommend removing the statement “ (b) (4) ” from the PDP of the syringe label.
PFS Blister Labeling			
1.	The linear barcode is missing.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25 (C)(2).	Add the linear barcode to the PFS blister labeling in accordance with 21 CFR 201.25 (C)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text, and in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

From the DMEPA1 review finalized on February 15, 2025:

CONCLUSION

Celltrion, Inc. implemented all of our recommendations. Additionally, we note that Celltrion proposes to represent the month as “MM” on their revised label and labeling. They included an image of the PFS as part of their information request response, which depicts that the expiration date will be represented using [REDACTED] ^{(b) (4)}.

We have no additional recommendations at this time.

From the Office of Prescription Drug Promotion (OPDP) review finalized on February 25, 2025:

The reviewer recommends that the Applicant update the cross references in the Highlights Dosage and Administration section.

8. Advisory Committee Meeting

No Advisory Committee was necessary or planned for this supplement.

9. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients 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.

The labeling for US- 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 for those indications. [REDACTED] ^{(b) (4)}

[REDACTED] Refer to Pediatric section in BMER dated on 6/27/2024 in DARRTS. There is no new pediatric information submitted for this resubmission. At this time, no pediatric studies are required under PREA for this BLA.

10. Other Relevant Regulatory Issues

None.

11. Labeling

Labeling will be deferred until the supplement is otherwise approvable.

12. Recommendations

We have completed the review of this BLA RESUBMISSION and have remaining concerns. The unresolved Product Quality and Facility Inspection concerns preclude approval of this BLA resubmission. The recommended regulatory action is a Complete Response, and the following comments will be issued to the applicant:

Facility Inspection

Following a pre-license inspection (PLI) of Thermo Fisher Scientific (Patheon Italia S.p.A.), Ferentino, Italy (FEI: 3004110157) 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. Satisfactory responses from the facility are needed before this application can be approved. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. The assessment of the 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 to resolve the related deficiencies.

Additional: The following deficiency should be included in the Complete Response letter but is **not an approvability comment.**



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
03/26/2025 01:22:00 PM

WILLIAM M BOYD
03/26/2025 01:55:48 PM

Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 Eydenzelt (afibercept-boav)

Proposed (b) (4) biosimilar to U.S.-Eylea

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	BLA 761377
IND Number	IND 147335
Received Date	June 29, 2023
BsUFA Goal Date	June 29, 2024
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Review Completion Date	See DARRTS stamped date
Product Code Name	CT-P42
Proposed Nonproprietary Name¹	Aflibercept-boav
Proposed Proprietary Name¹	EYDENZELT
Pharmacologic Class	vascular endothelial growth factor (VEGF) inhibitor
Applicant	Celltrion, Inc.
Applicant Proposed Indication(s)	Indicated for the treatment of patients with: <ul style="list-style-type: none">• Neovascular (Wet) Age-Related Macular Degeneration (AMD)• Macular Edema Following Retinal Vein Occlusion (RVO)• Diabetic Macular Edema (DME)• Diabetic Retinopathy (DR)
Recommendation on Regulatory Action	Complete Response

¹Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 CT-P42 (afibercept-boav)

Proposed (b) (4) biosimilar to US-licensed Eylea

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Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 CT-P42 (aflibercept-boav)

Proposed (b) (4) biosimilar to US-licensed Eylea

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351(k) BLA 761377 CT-P42 (aflibercept-boav)

Proposed (b) (4) biosimilar to US-licensed Eylea

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Reviewers of Biosimilar Multidisciplinary Evaluation and Review

Regulatory Project Manager	Dheera Semidey
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Cross-Discipline Team Leader(s) (CDTL(s))	Rhea Lloyd, M.D.
Designated Signatory Authority (DO/OSM)	William Boyd, M.D.

DO=Division of Ophthalmology

OSM=Office of Specialty Medicine

OTBB=Office of Therapeutic Biologics and Biosimilars

BLA 761377 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
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OTBB labeling and RPM	Ruby (Chi-Ann) Wu, Jacquelyn Rosenberger
Deputy Division Director	William Boyd
Deputy Office Director	Alex Gorovets
Office Director	Charles Ganley

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
US- EYLEA	US-approved Eylea
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat

Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 CT-P42 (aflibercept-boav)

Proposed (b) (4) biosimilar to US-licensed Eylea

MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
U.S.-Eylea	U.S.-licensed EYLEA

1. Executive Summary

1.1. Product Introduction

Celltrion Inc. (hereafter referred to as “Applicant” or “Celltrion”) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for CT-P42 as a proposed (b) (4) biosimilar to US-licensed Eylea (hereafter referred to as US-Eylea). The proposed proprietary name is Eydenzelt, and proposed non-proprietary name is aflibercept-boav. US- Eylea is available in 2 mg (0.05 mL of 40 mg/mL), injection, for intravitreal use in a single-dose prefilled syringe (PFS) and a single dose vial co-packaged with injection components (i.e., vial kit).

Celltrion is seeking licensure for the 2 mg (0.05 mL of 40 mg/mL) strength in a single-dose PFS and a single-dose vial co-packaged with injection components (i.e., vial kit). A 2 mg (0.05 mL of 40 mg/mL) dose is for the following indications which 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)

For neovascular (wet) age-related macular degeneration (AMD), CT-P42 2 mg (0.05 mL of 40 mg/mL) is recommended to be administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL of 40 mg/mL) via intravitreal injection once every 8 weeks (2 months). For macular edema following retinal vein occlusion (RVO), CT-P42 2 mg (0.05 mL of 40 mg/mL) solution is recommended to be administered by intravitreal injection every 4 weeks (approximately every 25 days, monthly). For diabetic macular edema (DME) and diabetic retinopathy (DR), CT-P42 2 mg (0.05 mL of 40 mg/mL) solution is recommended to be administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL of 40 mg/mL) via intravitreal injection once every 8 weeks (2 months). (b) (4)

The strength, dosage form, route of administration, indications and dosing regimens for CT-P42 will be the same as those of US-Eylea.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

Aflibercept is a recombinant human fusion protein consisting of portions of human VEGF receptors VEGFR-1 and VEGFR-2 extracellular domains fused to the constant region (Fc) of human IgG1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, which blocks the VEGFR downstream signaling cascade associated with pathological angiogenesis and vascular leakage. VEGF-A, VEGF-B, and PlGF are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF-A acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF and VEGF-B bind only to VEGFR-1, which is present on the surface of leucocytes as well as endothelial cells. Activation of the receptors by VEGF-A can result in neovascularization and vascular permeability. PlGF is also linked to neovascularization and recruitment of inflammatory cells into tumors.

This BLA contains sufficient data and information to demonstrate that CT-P42 has the same mechanism(s) of action as that of U.S.- Eylea (aflibercept) to the extent known. The applicant performed a comparative analytical assessment of CT-P42 and US-Eylea. The data provided support the conclusion that CT-P42 is highly similar to US-Eylea

U.S.-Eylea is licensed in 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use, in a vial kit and in a PFS. The Applicant is seeking licensure of CT-P42 for 2mg (0.05mL of 40mg/mL) injection, for intravitreal use in a vial kit and in a PFS. The strength of CT-P42 in each intravitreal injection is the same as that of U.S.-Eylea. CT-P42 also has the same dosage form and route of administration as that of U.S.-Eylea.

Additionally, the condition(s) of use for which the applicant is seeking licensure have been previously approved in the U.S.-Eylea.

1.4. Inspection of Manufacturing Facilities

Celltrion Inc. (FEI 3005241015) is responsible for the manufacturing, release, and stability testing of CT-P42 drug substance as well as release and stability testing of CT-P42 drug product. (b) (4) is responsible for the manufacturing of CT-P42 PFS. Separate Pre-License Inspection (PLI) was conducted by OPQ and ORA for the two sites. Celltrion was inspected between February 19 and February 27, 2024, and (b) (4) was inspected between (b) (4) and (b) (4). The inspection covered the firms Quality, Facilities and Equipment Production,

Material, and Laboratory Systems used in the manufacturing and testing of CT-P42 drug substance and drug product. The Agency conveyed deficiencies to the representative of each facility. See the OPQ Executive Summary assessment memo for the complete review.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from Study CT-P42 3.1, which used EU-approved Eylea as the non-US-licensed comparator product, to the assessment of biosimilarity. The Office of Pharmaceutical Quality (OPQ), CDER has determined, and I agree, that based on the data provided by the Applicant, the comparative analytical data establish the scientific bridge that justifies the relevance of comparative clinical data generated using EU- approved Eylea to the assessment of biosimilarity.

1.6. Biosimilarity (b) (4) Assessment

Table 1 below summarizes individual discipline recommendations regarding the adequacy of the data and information the Applicant submitted to support a demonstration of biosimilarity (b) (4).

Table 1 Summary and Assessment of Biosimilarity (b) (4)

Comparative Analytical Studies²	
Summary of Evidence	<ul style="list-style-type: none">• CT-P42 is highly similar to US-Eylea, notwithstanding minor differences in clinically inactive ingredients.• The comparative analytical data establish the scientific bridge that justifies the relevance of comparative data generated using EU-Eylea to the assessment of biosimilarity.• CT-P42 2 mg (0.05 mL of 40 mg/mL) in a PFS and 2 mg (0.05 mL of 40 mg/mL) in a vial kit are the same strength as that of US- Eylea in a PFS and in a vial kit.• The dosage form and route of administration is the same as that of US-Eylea
Assessment of Residual Uncertainties	<ul style="list-style-type: none">• There are no residual uncertainties from a product quality perspective.

²Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Animal/Nonclinical Studies	
Summary of Evidence	<ul style="list-style-type: none"> • A 12 week repeat- dose study was conducted using cynomolgus monkeys. FDA has determined that the animal studies are unnecessary in this 351(k) application. • Animal studies were not required to support this 351(k) application. • The information relating to toxicity supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	<ul style="list-style-type: none"> • There are no residual uncertainties from a non-clinical perspective.
Clinical Studies	
<i>Clinical Pharmacology Studies</i>	
Summary of Evidence	<ul style="list-style-type: none"> • 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 differences between CT-P42 and US-Eylea. • Comparable incidence of ADA/Nab formation between CT-P42 and EU-Eylea in patients with DME supports a demonstration that there are no clinically meaningful differences between CT-P42 and US-Eylea.
Assessment of Residual Uncertainties	<ul style="list-style-type: none"> • There are no residual uncertainties from a clinical pharmacology perspective.
<u>Clinical Studies</u>	
Summary of Evidence	<ul style="list-style-type: none"> • In Study CT-P42 3.1, the patients (n=348) with DME were treated with either CT-P42 or EU-Eylea. There were no meaningful differences in terms of efficacy or safety between CT-P42 and EU-Eylea. The data from this study support a demonstration of no clinically meaningful differences between CT-P42 and US-Eylea.
Assessment of Residual Uncertainties	<ul style="list-style-type: none"> • There are no residual uncertainties from the clinical or clinical statistical perspectives.

(b) (4)

Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 CT-P42 (afibercept-boav)

Proposed ^{(b) (4)} biosimilar to US-licensed Eylea

(b) (4)

Assessment of Residual Uncertainties	<ul style="list-style-type: none">• There are no residual uncertainties from a clinical or clinical statistical perspective.
Any Given Patient Evaluation	
Summary of Evidence	<ul style="list-style-type: none">• The Applicant has provided adequate data and information, including analytical and clinical data, to support a demonstration that CT-P42 can be expected to produce the same clinical result as that of US- Eylea in any given patient.
Assessment of Residual Uncertainties	<ul style="list-style-type: none">• There are no residual uncertainties from the clinical perspective.
Extrapolation	

<p>Summary of Evidence</p>	<ul style="list-style-type: none">• The information submitted in the original BLA supports a demonstration that CT-P42 and US-Eylea are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency.• The data and information provided by the Applicant are sufficient to demonstrate that CT-P42 can be expected to produce the same clinical result as US-Eylea in any given patient (b) (4)• Division of Ophthalmology (DO) has determined that the Applicant has provided adequate scientific justification and agrees with the Applicant's justification for extrapolation to the other indications listed in the US-Eylea package insert being sought for licensure based on: 1) the mechanism of action of aflibercept, including the structure and drug-target interactions in each condition is consistent across all approved indications. For each of the indications being sought for licensure, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, diabetic macular edema, diabetic retinopathy and retinopathy of prematurity by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and 2) the analysis of the known safety and immunogenicity profiles of aflibercept across each of the indications being sought is consistent and there are no known differences in expected toxicities for each indication.• The data and information submitted by the Applicant, including the justification for extrapolation, supports licensure of CT-P42 as (b) (4) biosimilar to US-Eylea for the following indications for which US-Eylea has been previously approved:<ul style="list-style-type: none">○ Neovascular (Wet) Age-Related Macular
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	<p>Degeneration (AMD)</p> <ul style="list-style-type: none"> ○ Macular Edema Following Retinal Vein Occlusion (RVO) ○ Diabetic Macular Edema (DME) ○ Diabetic Retinopathy (DR) <p>(b) (4)</p>
<p>Assessment of Residual Uncertainties</p>	<ul style="list-style-type: none"> ● There are no residual uncertainties from the clinical perspective.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that CT-P42 is highly similar to US-Eylea, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between CT-P42 and US-licensed Eylea in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, are sufficient to demonstrate that CT-P42 can be expected to produce the same clinical result as US-Eylea in any given patient (b) (4)

Therefore, the data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that:

- CT-P42, 2mg (0.05mL of 40mg/mL) injection, for intravitreal use in a PFS is biosimilar to (b) (4) US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a PFS,³ and
- CT-P42, 2mg (0.05mL of 40mg/mL) injection, for intravitreal use in a vial kit is biosimilar to (b) (4) US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and in a PFS

for each of the following indications for which US- Eylea has been previously approved and for which the Applicant is seeking licensure of CT-P42:

- Neovascular (Wet) Age-related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)

³

(b) (4)

- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

However, data submitted in this application is not sufficient to support a conclusion that the manufacture of CT-P42 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Additionally, the OPQ team has identified the drug product PFS microbiology control issues that preclude the approval of this application. Therefore, the FDA review team recommended a Complete Response for this application, and the CDTL and the Division Signatory agree with that recommendation. The Complete Response Letter will outline the deficiencies and the information and data required to address the deficiencies.

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Applicant sought guidance on the development program under Pre-Investigational New Drug Application (PIND) 147335 under drug code name CT-P42. **Table 2** below provides some highlights from the relevant interactions between FDA and the Applicant during product development for CT-P42.

Table 2 Interaction between FDA and Celltrion during CT-P42 drug product

Date	Interaction Type	Comment/Recommendations
6/22/2020	BPD Type 2	The Agency agreed on the proposed overall study design, and primary endpoint for the comparative clinical study. For the product quality aspects, the Agency recommended larger scale manufacturing of CT-P42 and provided additional microbiology comments. The Agency confirmed that no animal studies are needed to support clinical studies.
8/30/2021	BPD Type 2	For the proposed product quality, the Agency recommended assessment of worst-case sterilization conditions that impact CT-P42. The proposal to evaluate biocompatibility of PFS device was acceptable. The acceptability to support CAA will be a review issue in the BLA.

Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 CT-P42 (afibercept-boav)

Proposed (b) (4) biosimilar to US-licensed Eylea

		Strategy for immunogenicity testing was acceptable with recommendation to bank samples for future assessments.
05/18/2022	Advice/Information Request Letter	(b) (4)
8/15/2022	BPD Type 2	The Agency recommended CAA and product quality aspects including VEGF binding ELISA assay for DP and DS, DP stability testing, and leachable study for the container closure. It is clarified that CT-P42 is a combination product.
11/11/2022	iPSP	The Agency agreed to the iPSP.
1/31/2023	BPD Type 4	The Agency agreed on the contents and format to be submitted in a BLA and the approach to support (b) (4)
7/12/2023	Advice/Information Request Letter	The Agency provided clarification on information other than (b) (4)
7/19/2023	BPD Type 2a	The Agency clarified some administrative considerations for the sponsor to be aware of should they seek licensure of CT-P42 (b) (4)

2.2. Studies Submitted by the Applicant

Tables **below** list the studies submitted by the Applicant in support of a demonstration of biosimilarity between CT-P42 and US-Eylea. Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies.

Table 3 Listing Animal Studies Submitted

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/Dose
Animal Studies					
10r090	114831	Cynomolgus Monkey	5	1 month	Intravenous; 5 mg/kg

Table 4 Listing All Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study					
CT-P42 3.1 (Comparative efficacy and safety study)	04739306	<p>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</p> <p>Secondary: To evaluate additional efficacy, PK, usability (vial kit and PFS), and overall safety including immunogenicity</p>	multi-center, double-masked, randomized, active controlled, parallel group study to compare efficacy and safety of CT-P42 and EU-Eylea in patients with DME	Male or female patients 18 years old and older with DME	<p>Main Study Period (Double-masked, active controlled): 2 mg (0.05 mL of 40 mg/mL) of CT-P42 or EU-Eylea intravitreal injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses up to Week 52</p> <p>• Randomized: 348 patients - CT-P42: 173 - EU-Eylea: 175</p> <p>Extension Study Period (open-label, single arm) 2 mg (0.05 mL of 40 mg/mL) of CT-P42 intravitreal injection via a single-dose PFS at Extension Week 0</p> <p>CT-P42: 31 patients</p>

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

CT-P42, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a PFS and in a vial kit is a proposed (b) (4) biosimilar to US-licensed Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a PFS and in a vial kit for the same indications for which US-Eylea has been previously approved and for which the Applicant is seeking licensure of CT-P42. 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 (PIGF) 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

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endothelial cells. PIGF 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 PIGF, 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. 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 of Executive Summary for a summary of the CAA.

CT-P42 drug substance (DS) is manufactured at (b) (4) L scale in CHO cells. (b) (4)

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of BLA 761377 for CT-P42. The DS is manufactured at Celltrion Inc. (FEI 3005241015), PFS DP is manufactured at (b) (4), and the vial DP is manufactured at Patheon Italia SpA, Monza, Italy; FEI# 3003065803). During a recent inspection of the Celltrion Inc., Incheon, South Korea and (b) (4) manufacturing facilities for this application, our field inspectors conveyed deficiencies to the representative of the respective facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

Overall, the data submitted in this application are not sufficient to support a conclusion that the manufacture of CT-P42 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. OPQ is recommending that a Complete Response letter be issued to Celltrion Inc. to outline the deficiencies and the information and data that will be required to support approval.

3.2. Devices

CT-P42 PFS is a 0.5 mL (b) (4) syringes with (b) (4) rubber plunger stoppers and (b) (4) rubber luer lock tip caps with (b) (4).

CT-P42 vial is a glass vial (2 (b) (4) vial, type (b) (4) clear glass) with a stopper (13 mm, (b) (4) rubber) and a cap (13 mm, aluminum seal with a (b) (4)). The vial kit is co-packaged with injection components containing one 18-gauge x 1½ inch sterile filter needle (5µm), one 1 mL sterile Luer lock plastic syringe, and one 30-gauge x ½ inch sterile injection needle.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH recommends approval for the device constituent parts of the combination product.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA reviewed Celltrion's use-related risk analyses and comparative analyses between the proposed CT-P42 PFS and vial kit and the US-Eylea PFS and vial kit. They have concluded that no further information or data (e.g., data from a comparative use human factor study) is needed to support this marketing application. There are no human factors recommendations for this marketing application. Please refer to DMEPA review dated on 8/23/2023 in DARRTS.

DMEPA reviewed the proposed labels and labeling and concludes that labeling may be improved to promote the safe use of this product from a medication error perspective. They provided recommendations to improve clarity; however, labeling review will be deferred until next review cycle because of the Complete Response action for this application.

3.3. Office of Study Integrity and Surveillance (OSIS)

Not applicable

3.4. Office of Scientific Investigations (OSI)

Not applicable.

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The Applicant submitted the results of a 12-week cynomolgus monkeys study to evaluate and compare the toxicity between CT-P42 and US- Eylea (Study No. 84223006).

From a nonclinical perspective, because the toxicity of aflibercept products, barring differences in clinical parameters, is a direct function of their affinity to VEGF-A and PIGF and related activity, the comprehensive battery of in vitro cell-free and cell-based studies are considered more sensitive than animal studies in detecting functional differences and toxicities, should they exist, between CT-P42 and US-Eylea.

The applicant's development program was designed to support a demonstration that CT-P42 is highly similar to the US-Eylea using physicochemical and biological assays. Comparative analytical data between CT-P42 and US-Eylea was assessed by the Quality discipline. From a nonclinical perspective, the comparative analytical data show that CT-P42 is highly similar to US-Eylea and the final determination was made by the Quality discipline. In the absence of specific clinical, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity. In summary, no animal studies with CT-P42 and US-Eylea were needed to support this 351(k) application and the results of the in vitro studies support a demonstration of biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

CT-P42 drug product is a sterile, preservative free solution that is presented as a single-use vial kit and a PFS. Each vial and PFS contains 0.05mL solution that is designed to deliver 2 mg (0.05mL of 40mg/mL) dose of CT-P42 by intravitreal injection. The solution includes 0.038 mg (b) (4) Histidine, 0.033 mg L-Histidine monohydrochloride monohydrate, 0.038 mg Sodium chloride, 5mg trehalose, and 0.015 mg Polysorbate 20 at a pH 6.2. The formulation of CT-P42 is different from US-Eylea. The composition of CT-P42 is shown in the following Table 5.

Table 5 Composition of CT-P42 and US-Eylea

US-Eylea Formulation	CT-P42 Formulation
40 mg/mL aflibercept	40 mg/mL CT-P42
(b) (4) mM sodium phosphate	-
5% w/v sucrose	-
0.03% w/v polysorbate 20	0.03%w/v polysorbate 20
(b) (4) mM sodium chloride	(b) (4) mM sodium chloride
-	(b) (4) mM histidine (0.038 mg (b) (4) Histidine, 0.033 mg L-Histidine monohydrochloride monohydrate
-	10% trehalose
pH 6.2	pH 6.2

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No impurities of concern were identified.

The proposed commercial presentations are a single-dose prefilled syringe (PFS) and a single-use vial designed to provide 2mg (0.05mL of 40mg/mL) solution for intravitreal injection. CT-P42 single-use vial is co-packaged as follows:

- vial kit with injection components (18-gauge x 1½ inch sterile 5µm filter needle, 1 mL sterile Luer lock plastic syringe, and one 30 gauge x ½ inch sterile injection needle)

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Clinical Pharmacology Major Review Issues and Recommendation

Review Issue	Recommendation 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 comparable based on descriptive statistics, supporting a demonstration of no clinically meaningful differences between CT-P42 and US-Eylea.
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 a demonstration of no clinically meaningful differences between CT-P42 and US-Eylea.

5.1.1 Clinical Pharmacology Residual Uncertainties Assessment

There are no clinical pharmacology residual uncertainties regarding PK and immunogenicity assessments.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-US licensed Comparator Product

Not applicable.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

A PK similarity study using traditional PK endpoints, such as AUC and C_{max}, in healthy subjects is not considered to be feasible for the following reasons: 1) aflibercept is administered by intravitreal injection directly into the eye to treat diseases that are localized to the eye and the systemic exposures following intravitreal injection is low (i.e., negligible) and variable, and 2) the conduct of a PK study in healthy subjects is considered unethical due to the invasiveness of intravitreal injections. Therefore, a PK sub-study within the comparative clinical study was recommended to provide PK data in support of no clinically meaningful differences in systemic safety. The objective of the PK sub-study was to descriptively compare the peak serum study drug concentrations.

5.3.1. STUDY CT-P42 3.1

Clinical Pharmacology Study Design Features and Endpoints

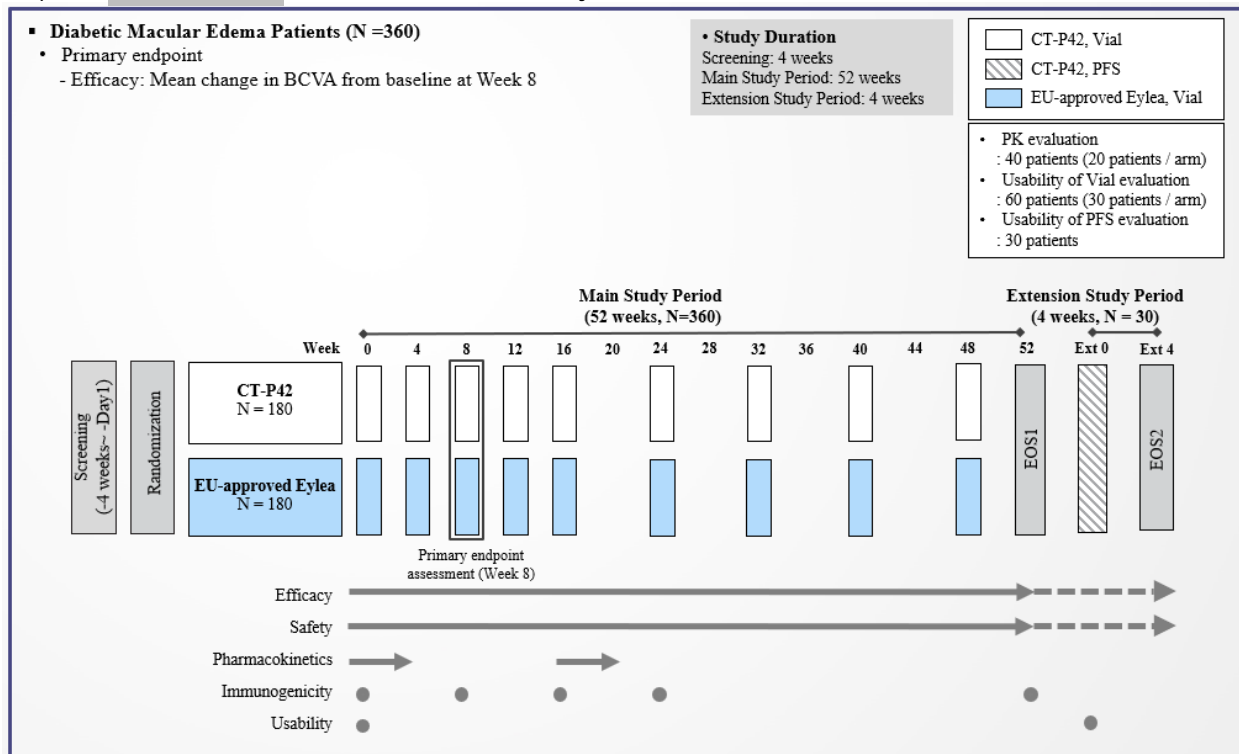
Study CT-P42 3.1 was a multicenter, double-masked, randomized, active-controlled, parallel-group study in subjects with diabetic macular edema (DME). A total of 348 subjects were randomized in a 1:1 ratio to receive either CT-P42 (2 mg (0.05 mL of 40 mg/mL)) or EU-Eylea (2 mg (0.05 mL of 40 mg/mL)) in the study eye by intravitreal injection using a single-dose vial kit once every four weeks for 5 doses, then every 8 weeks for 4 doses in the Main Study Period (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 intravitreal injection using a PFS in subjects with DME. A PK study comparing PK profiles of CT-P42 and EU-Eylea were descriptively evaluated in a subgroup of DME patients as part of comparative clinical study. The study design is illustrated in Figure 1 below.

Figure 1 Study Design of Study CT-P42 3.1

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Abbreviations: BCVA, Best Corrected Visual Acuity; EOS, end-of-study; Ext 0, Extension Week 0; Ext 4, Extension Week 4; EU, European Union; N = number of patients; PFS, prefilled syringe; PK, pharmacokinetics.

Note: The figure reflects the number of subjects that were planned, not the actual number of subjects that were evaluated.

Source: CSR CT-P42 3.1 Figure 9-1

Of the 348 subjects randomized, a PK sub-study was conducted in 23 subjects including 11 (3.2%) subjects in the CT-P42 group and 12 (3.5%) subjects in the EU-Eylea group. One subject was excluded from the PK population due to the war in Ukraine. The PK population includes those who received at least 1 full dose of study drug and provided at least one posttreatment PK sample in the Main Study Period.

PK samples were collected at pre-dose, 24 hours, 48 hours, and 72 hours after both the 1st and the 5th dose. The collected samples were analyzed for free (VEGF-unbound) study drugs. Blood samples for immunogenicity assessment were collected prior to study drug administration at Week 0 (Day 1), Week 8, Week 16, Week 24, and Week 52 (end-of-study [EOS]), or when immune-related adverse events (AEs) occurred.

The PK data were pre-specified to be analyzed qualitatively. The objective of the PK-sub study was to measure systemic exposure and compare the peak plasma concentrations of study drugs. Immunogenicity (incidence of ADA and Nab) was evaluated as one of the secondary endpoints.

Bioanalytical assay and performance for PK sample analysis

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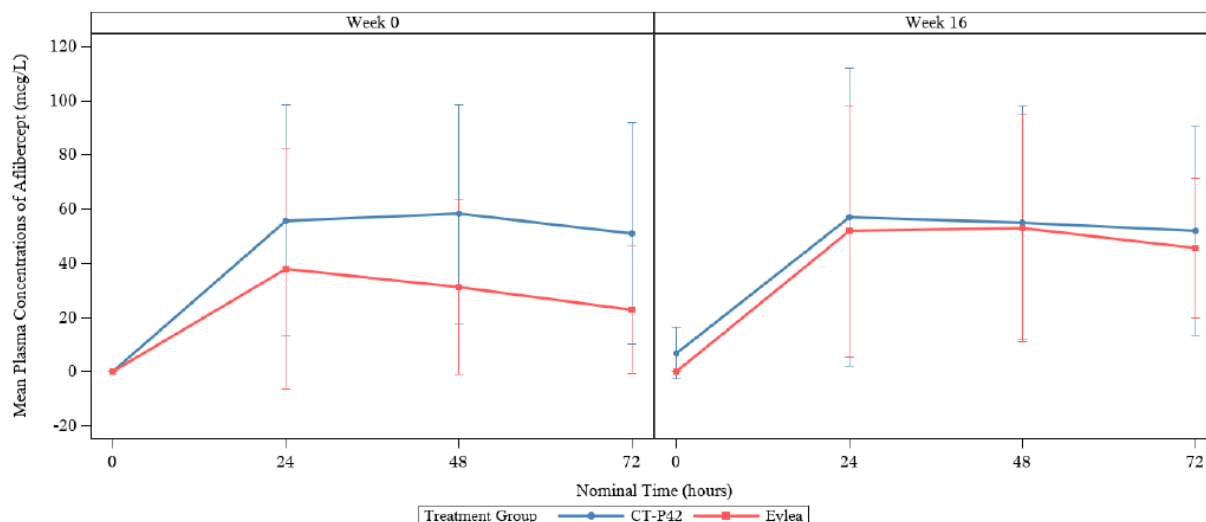
Plasma concentrations of study drugs were measured using a validated meso scale discovery (MSD)-electrochemiluminescence (ECL) immunoassay. The lower and upper quantification limits of the assay were 16 ng/mL and 1024 ng/mL, respectively. All PK samples were analyzed within the established stability period of 463 days (i.e., the maximum duration between sample collection and analysis was 322 days). Refer to Appendix for the clinical pharmacology review dated on 3/19/2024 in DARRTS regarding the bioanalytical assay validation and performance

PK of CT-P42 and EU-Eylea in subjects with DME

The graph of mean plasma concentration (+/- standard deviation (SD)) in CT-P42 group and EU-Eylea group at baseline and at Week 16 is shown in Figure 2. The descriptive statistics for plasma study drug concentrations and the PK parameters are presented in Table 1 and Table 2, respectively in the clinical pharmacology review memo (See review memo archived in DARRTS on 3/19/2024). The data showed that mean concentration of free study drugs measured systemically was similar across treatment arms following the first and fifth intravitreal injection at baseline and at Week 16, while the peak concentrations were observed after 24hrs post injection (both after 1st dose and 5th dose) in both treatment arms.

A high inter-subject variability in PK data was observed in both treatment groups. While the mean concentrations in the CT-P42 were numerically higher than the concentrations in EU-Eylea in general, clinical meaningfulness in terms of systemic safety of the observed difference is likely minimal. There are no meaningful differences in the systemic exposures that would have any implications on systemic safety following administration of CT-P42 and EU-Eylea in subjects with DME.

Figure 2 Mean (SD) Pharmacokinetic Profiles of Plasma Study Drug from baseline to Week 16



5.4. Clinical Immunogenicity Studies

Clinical immunogenicity assessment

Immunogenicity (ADA and NAb) was evaluated in all subjects in Study CT-P42 3.1 as one of secondary objectives. Refer to Section 5.3.1 for the detailed study design of Study CT-P42 3.1.

Samples for immunogenicity assessment were collected prior to study drug administration at Week 0 (Day 1), Week 8, Week 16, Week 24, and Week 52 (EOS), or when immune-related adverse events (AEs) occurred. Serum sample collected from immunogenicity assessment were first tested for ADA. Sample confirmed as positive for ADA were further tested for NAb.

The Applicant developed suitable binding and neutralizing antibody assays (ECL immunoassay) for detecting ADA and Nab in the presence of expected levels of CT-P42 and EU-Eylea.

The sampling timepoints were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation.

Comparison of Incidence of ADA and NAb

The immunogenicity results show that, in the overall, the incidence of positive ADA was low in both treatment groups and was comparable between the treatment groups. The incidence of ADA positive after the first study drug administration was 1.7% in both the CT-42 and EU-Eylea treatment groups. The incidence of NAb was also low. Two (1.2%) subjects in the CT-P42 group and 1 (0.6%) subject in the EU-Eylea group showed NAb positive result at post-

treatment visit. All patients with ADA positive results showed low ADA titer. The mean and the median ADA titer results were generally similar between the two treatment groups at each visit.

Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

None of the subjects who participated in the PK sub-study had positive ADA results. Therefore, the impact of immunogenicity on PK could not be assessed.

The primary comparative efficacy endpoint of Study CT-P42 3.1 is the change from baseline in BCVA at Week 8 with CT-P42 and EU-Eylea treatments. At Week 8, only 3 objects in the CT-P42 group and 2 objects in EU-Eylea group had positive ADA result. Low ADA incidences and high variability in data prevent the conclusion regarding the impact of immunogenicity on efficacy.

There was a total of 6 subjects who were tested ADA positive after drug administration. Among those 6 subjects, 3 subjects experienced at least 1 treatment emergent adverse event (TEAE); however, none of these TEAEs were study-drug related. As the incidence of ADA positive was very low, no conclusion could be made regarding the impact of immunogenicity on safety.

6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The clinical program includes, CT-P42 3.1, a clinical comparative efficacy and safety study with an imbedded pharmacokinetic (PK) subset study in patients with diabetic macular edema (DME). The primary efficacy analysis was conducted to assess whether there is any meaningful difference between CT-P42 and EU-Eylea in change in BCVA from baseline to Week 8. The pre-specified similarity margin was set as [-3, 3] letters.

The adjusted mean changes in BCVA from baseline at Week 8 were comparable between the two treatment groups. Based on both full analyses set (FAS) and per-protocol (PP) analysis set, the adjusted mean differences were 0.58 letters and 0.38 letters with 90% CIs of (-0.52, 1.67) letters and (-0.70, 1.45) using FAS and PP set, respectively, which were contained within the pre-specified similarity margin [-3, 3]. Thus, the study demonstrated the similarity of CT-P42 and EU-Eylea for the primary endpoint in both FAS and PP set.

The results support a demonstration of no clinically meaningful difference between CT-P42 and US-Eylea.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the statistical and clinical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. STUDY CT-P42 3.1

Data and Analysis Quality

No major issues were identified regarding the quality and integrity of the submitted SDTM and ADaM datasets under BLA 761377. The data quality control/assurance procedures are properly documented in the CSRs. The Applicant's primary efficacy results are reproducible using the ADaM datasets.

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

Study CT-P42 3.1 was a multi-center, randomized, double-masked, active-controlled, parallel group, comparative clinical study to demonstrate that there is no meaningful difference between CT-P42 and EU- Eylea in subjects with diabetic macular edema with respect to efficacy. The primary objective was to demonstrate the similarity of CT-P42 and EU-Eylea over 8 weeks, as assessed by change from baseline to Week 8 in best corrected visual acuity (BCVA) using the early treatment of diabetic retinopathy study (ETDRS) protocol. The secondary objective of this study was to evaluate additional efficacy, pharmacokinetics (PK), usability, and overall safety including immunogenicity.

This study was conducted in 83 centers across 13 countries (Czech, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Russia, Slovakia, Spain, Ukraine, Republic of Korea, and India).

The randomization 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).

The study consists of 3 periods:

- 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): prefilled syringe open-label evaluation (the second end-of-study visit).

During the Main Study Period, a total of 348 subjects were randomized in a 1:1 ratio to CT-P42 arm (N = 173) or EU-Eylea arm (N = 175). The schedule of activities is presented in Figure 1. During the study, subjects received either CT-P42 or EU-Eylea via intravitreal

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injection with a single-dose vial at 4-week intervals for the initial 5 doses, followed by a transition to 8-week interval for the subsequent 4 doses (baseline, Week 4, Week 8, Week 12, Week 16, Week 24, Week 32, Week 40, and Week 48). The Week 8 assessment corresponds to the primary endpoint evaluation time. Subjects were followed up to Week 52 for mean changes of BCVA and safety analysis.

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

Refer to Figure 1 see the schematic of the study design.

6.2.2. Statistical Methodologies

For a detailed discussion on the statistical methods, refer to the statistical review in DARRTS archived on 2/28/2024.

Analysis populations

The Applicant defined the following analysis sets for the Main Study Period:

- The intention-to-treat (ITT) set includes all subjects who were randomly assigned to receive either of the study drugs (CT-P42 or EU-Eylea), regardless of whether any study drug was administered.
- Safety set for Main Study Period includes all randomized subjects who received at least one full or partial dose of study drug in the main study period.
- The full analysis set (FAS) includes all randomized subjects who receive at least one full dose of study drug during the main study period. The FAS is the primary analysis set for efficacy endpoint analyses.
- The per-protocol (PP) set includes all randomized subjects who received all full doses of study drug up to Week 4 (total 2 injections), had a BCVA assessment at Week 8, and had no major protocol deviations which may affect the interpretation of study results of primary efficacy endpoint. Supportive analyses for the efficacy analyses are performed on the PP analysis set.
- Usability Set for Vial Kit includes all patients in the safety set who have evaluable usability measurements at Week 0. The usability set for vial kit was used for the usability analysis of CT-P42 vial kit for CT-P42 and EU-Eylea treatment groups.

The following analysis sets is used for analysis in the Extension Study Period:

- Safety Set for Extension Study Period includes all patients who receive a full 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 for PFS collected on or after Extension Week 0.

- Usability Set for PFS includes 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.

Sample size determination

The sample size calculation was based on the following assumptions: 1) similarity margin of [-3, 3] letters; 2) no expected mean difference between two treatment groups; 3) standard deviation (SD) of 8.2 letters; 4) 89% power; 5) 90% two-sided confidence interval (significance level of 5%).

With the assumptions, a sample size of 158 subjects per study group (316 subjects in total) was required to achieve a desired power of 89%. After considering 12% dropouts, a total of 360 subjects was planned for the study.

Analysis of primary endpoint

The primary endpoint is the change from baseline in BCVA by ETDRS letters at Week 8. An analysis of covariance (ANCOVA) model was used including the baseline BCVA and country as covariates, and treatment group as a factor only for study eye. The 2-sided 90% CI for the mean differences in the change from baseline and Week 8 in BCVA between the treatment groups (CT-P42 and EU-Eylea) was calculated using the least-squares mean and error estimates derived from ANCOVA. If 90% confidence interval for the mean differences is contained within the pre-defined similarity margin of [-3, 3] letters, similarity of CT-P42 and EU-Eylea could be concluded for the primary efficacy endpoint ($\alpha = 0.05$).

Analysis of secondary endpoints

- Change in BCVA using the ETDRS chart from baseline
- Change in CST from baseline as determined by spectral-domain OCT
- Subjects who gained ≥ 5 , ≥ 10 , and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS
- Subjects who lost ≥ 5 , ≥ 10 , and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS
- Patients with ≥ 2 -step improvement from baseline in the ETDRS DRSS score as assessed by FP.
- Clinical usability assessment for CT-P42 vial kit and CT-P42 PFS

6.2.3. Subject Disposition, Demographics and Baseline Characteristics

A total of 348 subjects were randomized in two groups: 173 subjects in CT-P42 and 175 subjects in EU-Eylea. There was no difference between ITT set and FAS set. Of the randomized subjects (ITT analysis set), 16 subjects were excluded from the PP analysis set. 169 subjects (97.7%) in CT-P42 group and 172 subjects (98.3%) in EU-Eylea group in the FAS set were remained in the study and conducted the primary endpoints assessment at Week 8. A total of 13 subjects (3.7%) discontinued from the study on or before Week 24, 5 (2.9%) subjects from CT-P24 group and 8 (4.6%) subjects from EU-Eylea groups. The most common reasons for discontinuation from the study among all randomized subjects were withdrawal of consent (1.4%) and adverse event (1.1%). All randomized patients had at least one DM history and at least one DME history. A significant proportion of patients (65.8%, 229/348) exhibited a baseline HbA1c level of $\leq 8\%$. Overall, DM and DME history were similar between the two treatment groups. HbA1c values were consistent between treatment groups. The average age of the subjects was 62.7 years of age. 58.3% (203/348) were male, and 224 individuals (64.4% of the total) were white. Majority are identified as non-smokers (70.4%, 245/348). At baseline, most patients (72.7%, 253/348) had a BCVA score of ≥ 55 letters. In general, the demographic, and stratification details were reasonably well balanced and comparable between the two treatment groups.

The detailed information on patient disposition, demographic and baseline characteristics refer to the clinical review in DARRTS archived on 6/27/24.

6.2.4. Results and Conclusions

Analysis of Primary Clinical Endpoint(s)

The objective of the primary endpoint analysis was to demonstrate the similarity of CT-P42 and EU-Eylea for the mean change in BCVA using the ETDRS chart from baseline to Week 8 with a similarity margin of ± 3 letters. The primary efficacy analysis was conducted on the FAS using an ANCOA model and a supportive analysis for the primary efficacy endpoint was conducted using the PP set.

Table 6 presents the primary endpoints analysis results. The mean changes in BCVA at Week 8 were comparable for the two treatment groups both in the FAS set and PPS set. The estimate of treatment differences in LS mean were 0.58 letters and 0.38 letters with 90% CIs of (-0.52, 1.67) and (-0.70, 1.45) letters for FAS and PP set, respectively, which were contained within the similarity margin of [-3, 3] letters. Therefore, similarity between CT-P42 and EU-Eylea was demonstrated for the primary endpoint. The results support no differences clinically between CT-P42 and EU-Eylea.

Table 6 Statistical Analysis of Mean Change from Baseline in BCVA at Week 8 by Treatment (ANCOVA)

Treatment	n	LS Mean (SE)	Estimate of Treatment Difference in LS Means (CT-P42 – Eylea)	90% CI
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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.

Sensitivity Analysis

There are total of 7 (2.0%) subjects (4 subjects in CT-P42 group, 3 subjects in EU-Eylea group) who had missing BCVA assessments at Week 8 for the primary efficacy analysis. To assess the impact of missing data, different sensitivity analyses were conducted to evaluate robustness of the primary analysis results. All subjects with non-missing baseline BCVA in FAS set is included in the analysis. The summary of sensitivity analysis results is presented in Table 7. The results show that in all of imputation/model the 90% CI for the estimate of treatment differences in LS mean at Week 8 between CT-P42 and EU-Eylea are also contained within the similarity margin of [-3, 3] letters, which were consistent with the primary analysis results, supporting the robust findings of similarity between CT-P42 an EU-Eylea.

Table 7 Sensitivity analyses for the primary endpoint

Analysis Population	Method	LS Mean (SE)		Difference (CT-P42 - Eylea)	
		CT-P42 (N = 173)	Eylea (N = 175)	Mean (SE)	90% CI
FAS	MI with the MAR assumptions ^[1]	9.44 (0.799)	8.84 (0.775)	0.60 (0.663)	(-0.49, 1.69)
FAS	MMRM ^[2]	9.36 (0.725)	8.76 (0.721)	0.60 (0.638)	(-0.45, 1.65)
FAS	ANCOVA using a conservative approach ^[3]	9.67 (1.320)	9.82 (1.280)	-0.151 (1.090)	(-1.95, 1.65)

^[1] The applicant’s method

^[2] The reviewer’s method. MMRM with treatment, visit, treatment-by-visit interaction, and country as fixed effects and baseline BCVA as a covariate.

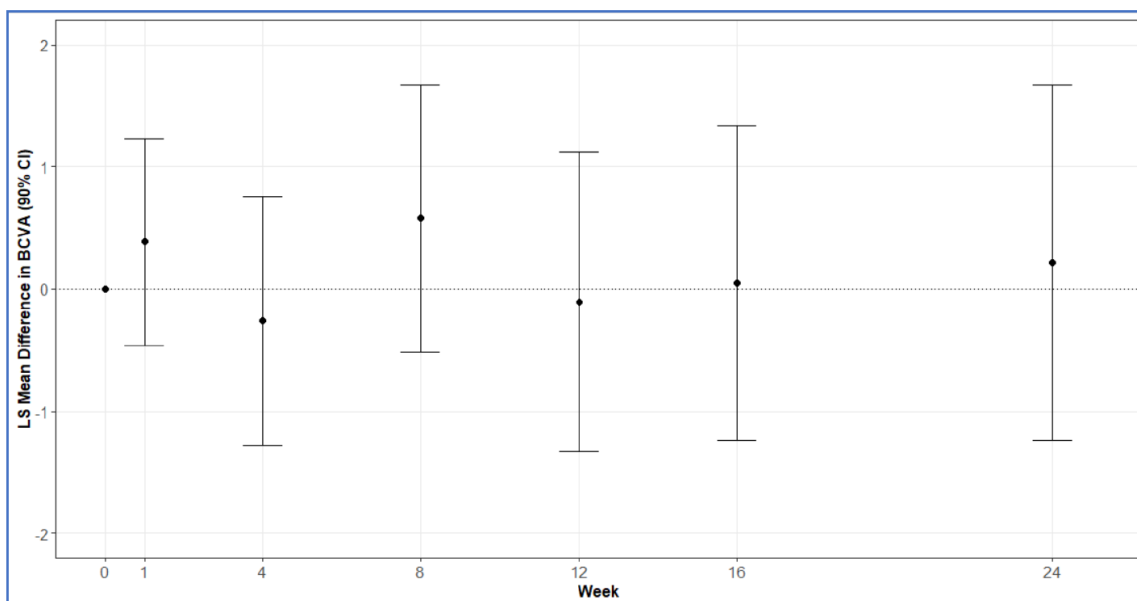
^[3] The reviewer’s method. Missing data was imputed using a conservative approach as described in “Sensitivity analysis for the primary endpoint” section.

Source: Reviewer’s analysis

Analysis of Secondary Clinical Endpoint(s)

Several of secondary endpoints and subgroup studies were analyzed. For mean change in BCVA from baseline up to Week 24, the differences in adjusted mean changes for CT-P42 and EU-Eylea in BCVA is shown in Figure 3. Consistent with the result from the primary endpoint analysis, the data indicated that all 90% CI are contained within the similarity margin of [-3, 3] letters from baseline up to Week 24.

Figure 3 Plot for mean change in BCVA with 90%CI from baseline to Week 24 (FAS)



ANCOVA with treatment as factor, and baseline BCVA and country as covariates using FAS.
Source: Reviewer's analysis

Usability Study Analysis

To support the licensure of CT-P42 vial kit and PFS presentation, the clinical usability study for the CT-P42 vial kit and CT-P42 PFS were incorporated in the Main Study Period and Extension Study Period of Study CT-P42 3.1, respectively. The objective of the usability study is to evaluate the healthcare professionals' ability to successfully administer the intravitreal injections to patients using the proposed vial kit or proposed PFS using the respective dosing and administration instructions while maintaining aseptic conditions in the intended use environment and document any use errors on all tasks.

The usability study is analyzed as part of the secondary clinical endpoint. The analysis populations include the Usability Set for vial kit and Usability Set for PFS. The endpoints including number of injections successfully administered by healthcare professionals with the proposed vial kit at Week 0 in the Main Study Period or proposed PFS at Extension Week 0, respectively.

The use of the proposed vial kit was evaluated at Week 0 in 95 patients (45 and 50 patients in the CT-P42 and EU-Eylea groups, respectively). 95 injection procedures were conducted. For the usability study that was conducted using the CT-P42 PFS presentation, 30 patients were administered (30 injection procedures) using a single-dose PFS in the Extension Week 0. All injections either with the proposed vial kit or proposed PFS were successfully administered without any use errors or close calls. The successful injection rate was 100% both for CT-P42 vial kit and CT-P42 PFS.

6.3. Review of the Safety Data

There is no integrated assessment of safety across the study as the application includes only a single comparative clinical study (CT-P42 3.1) to support the safety assessment of CT-P42. The safety of CT-P42 was evaluated in a single randomized, double-masked, active controlled study compared to EU-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 one full or partial dose of study drug. A 4-Month Safety Update 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).

6.3.1. Overall Exposure

Overall, 348 patients with DME (174 patients each in the CT-P42 and EU-Eylea group) received study treatment. The majority of patients in each treatment group had study drug administered as planned. Of these, 154 (88.5%) in the CT-P42 group and 152 (87.4%) in EU-Eylea group completed all 9 doses of study drug over the 52-week study duration. For all scheduled dose weeks, the proportions of patients who had the dose administered were comparable among the treatment groups. The mean (SD) of total number of doses received was 5.8 [0.7] doses in the CT-P42 group and 5.8 [0.8] doses in the EU-Eylea group up to Week 24. At the final analysis, the mean (SD) of total number of doses received increased to 8.5 (1.4) in CT-P42 group and 8.4 (1.6) in EU-Eylea group, respectively.

Adequacy of the safety database

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

6.3.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

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

Categorization of Adverse Events

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

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for AE (both ocular and non-ocular) and medical history were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. 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.

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.

6.3.3. Safety Results

There were 5 deaths reported during the Main study Period with 3 from those who received CT-P42 and 2 from those who received EU- Eylea. None of the causes of death are related to study drug. There were no ocular serious adverse events reported during the study. 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%). The total number of patients with one or more non ocular TEAEs was about 50% in both treatment groups with an infectious etiology, i.e., COVID, influenza, and nasopharyngitis, being the most common (13% in the CT-P42 vs. 16% in the EU-Eylea group). The rates of non-ocular adverse events were similar between the treatment groups as well. The total number of patients with one or more ocular TEAEs was 18-22% in both treatment groups with cataract, conjunctival hemorrhage, and increase intraocular pressure as the most common (12% in the CT-P42 vs 15% in the EU-Eylea group). Refer to Clinical review in DARRTS dated 6/27/2024.

Clinical Conclusions

Study CT-P42 3.1 demonstrated that CT-P42 and EU-Eylea have comparable efficacy and safety profiles including the change in best corrected visual acuity from baseline to Week 8, safety and immunogenicity. Safety was assessed in 348 subjects treated with intravitreal injections of CT-P42 and EU-Eylea over 52 weeks. Treatment with CT-P42 is considered safe with an adverse event profile similar to EU- Eylea. The adverse events seen were consistent with those seen with most intravitreally administered ophthalmic drugs. Overall, the comparative safety data support a demonstration that there are no meaningful differences between CT-P42 and EU-Eylea.

6.4.

(b) (4)

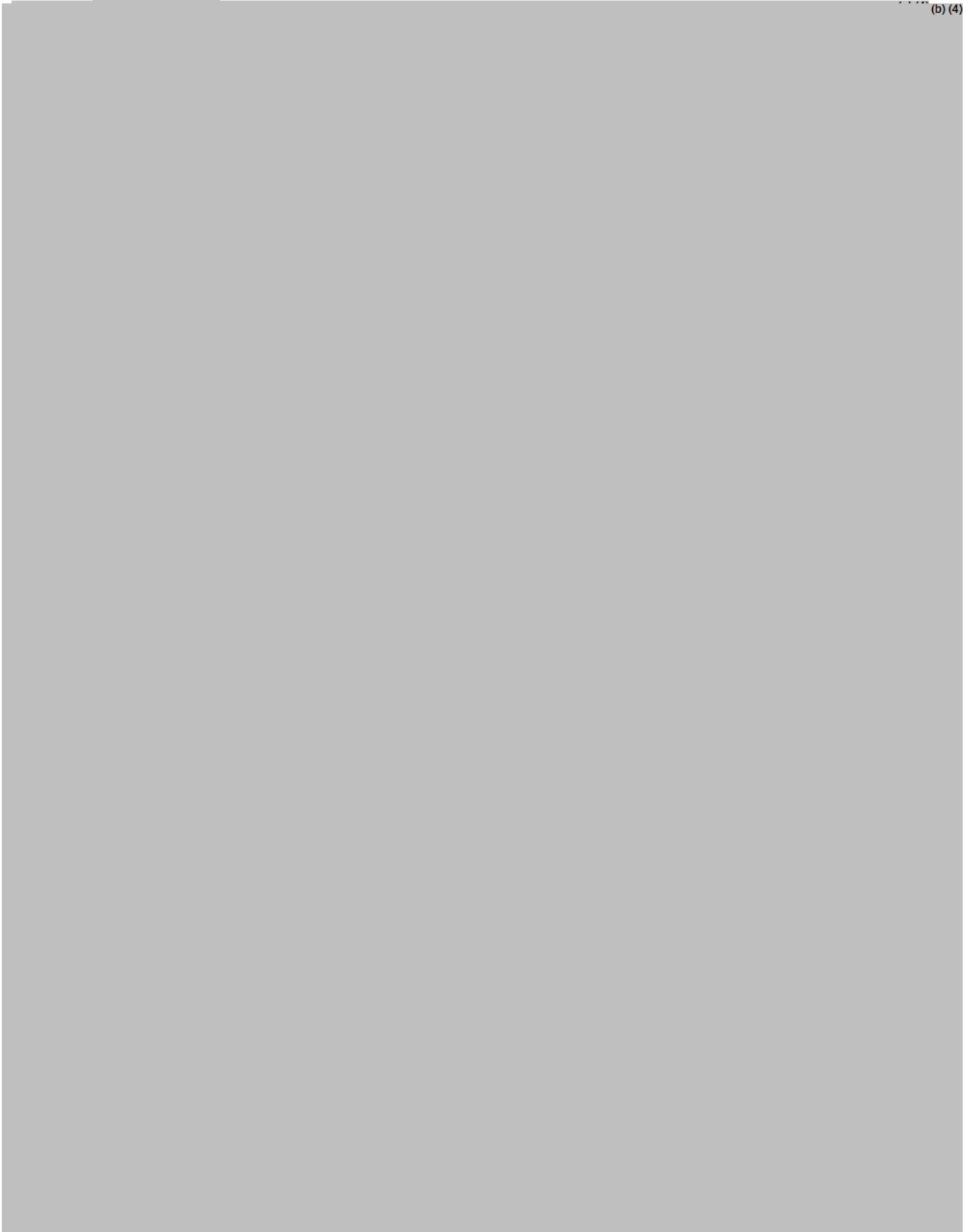
(b) (4)

Biosimilar Multidisciplinary Evaluation and Review (BMER)

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(b) (4)



6.5. Extrapolation

The Applicant submitted data and information in support of a demonstration that CT-P42 is highly similar to US- Eylea notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between CT-P42 and US- Eylea in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that CT-P42 can be expected to produce the same clinical results as US-Eylea in any given patient (b) (4)

The Applicant is seeking licensure of CT-P42 for the following indication(s) for which US-Eylea has been previously licensed and for which CT-P42 has not been directly studied: macular edema following retinal vein occlusion (RVO), neovascular (Wet) age-related macular degeneration (AMD) and diabetic retinopathy (DR).

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of CT-P42 as a (b) (4) biosimilar for each such indication for which licensure is sought and for which US-Eylea has been previously approved. Note that the Applicant is not seeking licensure for Retinopathy of Prematurity (ROP) (b) (4)

Therefore, the totality of the evidence provided by the Applicant supports licensure of CT-P42 as a (b) (4) biosimilar to US-Eylea for each of the following indication(s) for which the Applicant is seeking licensure of CT-P42: neovascular (Wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR).

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, CT-P42 is aflibercept-boav, was found to be conditionally accepted by the Agency on April 2, 2024.

7.2. Proprietary Name

The proposed proprietary name for CT-P42 is conditionally approved as Eydenzelt. This name has been reviewed by DMEPA, who concluded the name was acceptable.

7.3. Other Labeling Recommendations

In view of the recommendation for a Complete Response, the final labeling review will be deferred.

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized. Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki. The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.3 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the Applicant.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

10. Pediatrics

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

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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)

(b) (4) 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.

11. Recommendations for Risk Evaluation and Mitigation Strategies

None.

12. Recommendations for Postmarket Requirements and Commitments

None.

13. Comments to Applicant

A Complete Response is recommended 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)

Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 CT-P42 (aflibercept-boav)

Proposed (b) (4) biosimilar to US-licensed Eylea

(b) (4)

2.

3.

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. Following 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 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. 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 (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

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

3. 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.

Additional Microbiology comments

We have the following comments/recommendations that are 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 (b) (4). 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 (b) (4), frequency and duration of this potential CCI breach or whether the event has any CCI impact.

14. Financial Disclosure

Covered Clinical Study A randomized, active-controlled, double-masked, parallel group, phase 3 study (Study CT-P42 3.1) to compare efficacy and safety of CT-P42 in comparison with EU-approved Eylea® in patients with Diabetic Macular Edema (DME)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified:	83 Principal Investigators, 395 Sub-Investigators	
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: _____		

Biosimilar Multidisciplinary Evaluation and Review (BMER)

351(k) BLA 761377 CT-P42 (aflibercept-boav)

Proposed (b) (4) biosimilar to US-licensed Eylea

Proprietary interest in the product tested held by investigator: _____		
Significant equity interest held by investigator in S		
Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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/

DHEERA K SEMIDEY
06/27/2024 02:20:59 PM

MILALYNN S VICTORINO
06/27/2024 02:27:06 PM

MICHELLE T LUO
06/27/2024 02:29:35 PM

RHEA A LLOYD
06/27/2024 02:31:27 PM

WILLIAM M BOYD
06/27/2024 02:35:50 PM

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: <ul style="list-style-type: none"> • 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: <p>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</p> <ul style="list-style-type: none"> • 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. <p>Macular Edema Following Retinal Vein Occlusion (RVO)</p> <ul style="list-style-type: none"> • The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). <p>Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)</p> <ul style="list-style-type: none"> • The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks

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	<p>(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).</p> <ul style="list-style-type: none"> 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

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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

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NAb	neutralizing antibody
NPDR	non proliferative diabetic retinopathy
OE	ophthalmological examination

PD	Pharmacodynamic
PDR	proliferative diabetic retinopathy
PEDF	pigment epithelium derived factor
PK	Pharmacokinetic
PIGF	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 were 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
<u>Analysis of Condition</u>	<p>The following conditions if untreated will lead to visual loss:</p> <ul style="list-style-type: none"> • Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy 	<p>Aflibercept has been approved to treat the listed conditions in the US and has been shown to prevent visual loss.</p>
<u>Current Treatment Options</u>	<p>Lucentis (ranibizumab injection), Eylea (aflibercept), Beovue (brolocizumab), Byooviz (ranibizumab), Macugen (pegaptanib sodium injection) and Visudyne (verteporfin for injection). Avastin (bevacizumab) is used off-label to treat nAMD.</p>	<p>CT-P42 will add to the armamentarium of drugs to treat several retinal diseases that lead to vision loss.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	Eylea (aflibercept) is approved for the treatment of: <ul style="list-style-type: none"> • 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.
<u>Risk and Risk Management</u>	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)

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

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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 (pegaptanib sodium injection)	<ul style="list-style-type: none"> • Neovascular (wet) age-related macular degeneration
125156	Lucentis (ranibizumab injection)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Retinopathy (DR) • Myopic Choroidal Neovascularization (mCNV)
761125	Beovu (brolucizumab-dbl)	<ul style="list-style-type: none"> • Neovascular (Wet) Age-Related Macular Degeneration (AMD)

NDA/BLA	Drug Name	Indication
		<ul style="list-style-type: none"> • Diabetic Macular Edema (DME)
761235	Vabysmo (faricimab-svoa)	<ul style="list-style-type: none"> • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Diabetic Macular Edema (DME)
761165	Cimerli (ranibizumab-eqrn)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • Neovascular (Wet) Age-Related Macular Degeneration (AMD)
761350	Opuviz (aflibercept-yszy)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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.

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

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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 (afibercept-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 afibercept. 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.

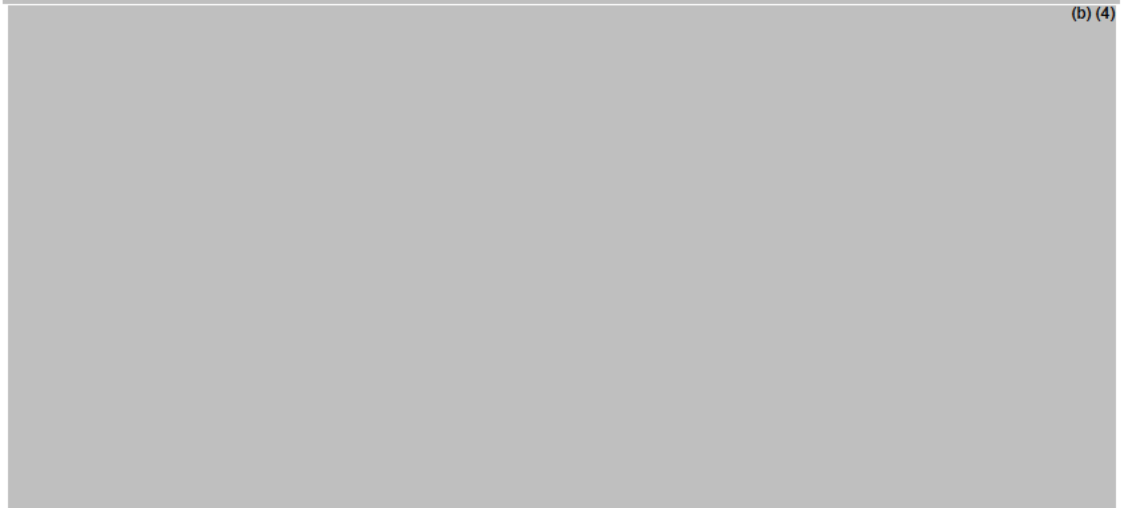
Microbiology

1.



(b) (4)

2.



(b) (4)

3.

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

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

2. 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.
3. 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.

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 (b) (4)

(b) (4). 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 (b) (4), 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. (b) (4) 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 (b) (4); Testing of the (b) (4)	No Evaluation Necessary

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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

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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 of 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)

(b) (4)

The initial field recommendation for BLA 761377 was “withhold” due to the objectionable conditions related to (b) (4) practices and facility design. The recommendation was upheld during compliance review.

In addition, an inspection of the (b) (4) facility (FEI# (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.

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

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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.
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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

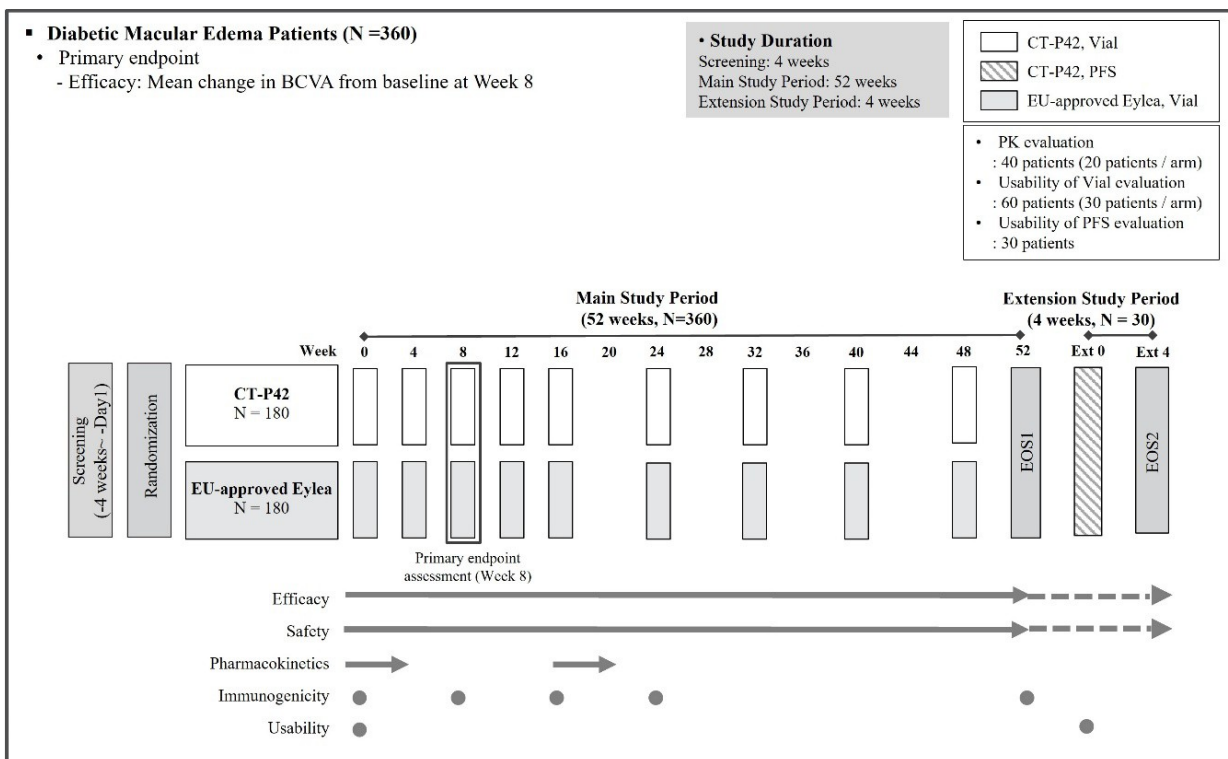
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letters versus ≥ 55 letters) using the ETDRS chart on Day 1; country; and PK subgroup (Yes versus No).

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

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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

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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. Therasas 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. Waryńskiego 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, Ophthalmology, Piaseczno, 05-500 Poland	1
Marta Misiuk-Hojlo	2518	Uniwersytecki Szpital Kliniczny ul. Borowska 213, Oddział Okulistyki, Budynek A, II pietro, Wroclaw, 50-556 Poland	1

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Investigator	Site Number	Site Address	Randomized Subjects
Russian Federation			
Alena Eremina	2804	Novosibirsk Branch of FBSI IRTC 10 Kolkhidskaya street, Novosibirsk, 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

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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 BLES 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 Serhienko	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 \geq 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 \geq 160 mmHg or diastolic \geq 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)

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.

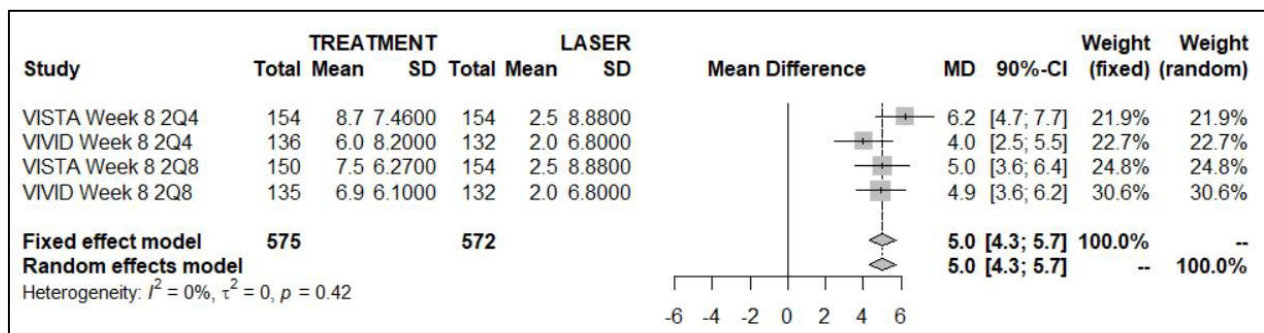
The primary efficacy analysis was conducted on the FAS, and the primary endpoint was also analyzed using the PP set as a supportive analysis. The sensitivity analysis was performed in the FAS to evaluate the impact of missing data on the primary efficacy result. Missing data was imputed using multiple 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 C_{max1}, C_{max2}, T_{max1}, and T_{max2} 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.

Clinical Review
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- 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.

- 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 μ m. 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.
- 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 status¹, 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 HbA1c², 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

- Percentages were calculated by using the number of female patients.
- 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.

Clinical Review
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CT-P42 (aflibercept-boav)
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 HbA1c², 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)

Subgroup	CT-P42 (N=173)		Eylea (N=175)	
	Actual Result	Change From Baseline	Actual Result	Change From 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 Statistic	Actual Result	Change From Baseline	Actual Result	Change From 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)	(b) (6)	(b) (6)	Dyspnea	Unrelated
(b) (6)	85/F/W	(b) (6)	(b) (6)	(b) (6)	Cardiac arrest	Unrelated
(b) (6)	71/F/W	(b) (6)	(b) (6)	(b) (6)	Pneumonia	Unrelated
EU-Eylea treatment group						
(b) (6)	83/M/W	(b) (6)	(b) (6)	(b) (6)	Death	Unrelated
(b) (6)	58/M/W	(b) (6)	(b) (6)	(b) (6)	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%)
Hyperkalemia	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%)

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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	CT-P42 (N=174)	EU-Eylea (N=174)
ADA Result	Number (%) of patients	
NAb Result		
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.

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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 <input checked="" type="checkbox"/>	No <input type="checkbox"/> (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): <u>none</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>none</u>		
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 <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (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

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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.

2.

3.

(b) (4)

4.

(b) (4)

5. Following review of DMF [REDACTED] (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 [REDACTED] (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

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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 [REDACTED] (b) (4)
[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.

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

Office of Clinical Pharmacology Review

NDA Number	761377
Link to EDR	\\CDSESUB1\evsprod\BLA761377\0001
Submission Date	6/29/2023
BSUFA Goal Date	6/29/2024
Submission Type	New BLA (biosimilar)
Drug Name	EYDENZELT (CT-P42) – proposed biosimilar to Eylea (aflibercept)
Dosage Form and Strength	Solution (40 mg/mL) in a glass vial and in a pre-filled syringe (PFS)
Route of Administration	Intravitreal
Proposed Indication	Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)
Proposed Dosage Regimen	2 mg (0.05 mL) via intravitreal (IVT) injection once a month (approximately 28 days)
Applicant	CELLTRION, Inc.
Associated IND	135944
OCP Review Team	Soo Hyeon Shin, Pharm.D., Ph.D. Ping Ji, Ph.D.
OCP Division	Division of Inflammation and Immune Pharmacology

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1. EXECUTIVE SUMMARY

The Applicant developed CT-P42, a proposed biosimilar to US-Licensed Eylea® (aflibercept). Aflibercept is a vascular endothelial growth factor (VEGF) inhibitor which binds to VEGF-A and placental growth factor (P1GF) thereby inhibiting the binding and activation of these cognate VEGF receptors. The proposed indications are the same as those approved for US-licensed Lucentis, except for Retinopathy of Prematurity (ROP) which is under orphan drug exclusivity protection, and are listed below:

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

The clinical development program to support this biosimilar application included a phase 3, double-masked, randomized, active-controlled, parallel-group study (CT-P42 3.1) in subjects with DME. The study was designed to compare the efficacy, PK, usability and overall safety including immunogenicity of CT-P42 compared with EU-Eylea. Clinical pharmacology data in this BLA includes PK data in a subset of subjects and immunogenicity data in all subjects from Study CT-P42 3.1.

1.1 Recommendations

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.

1.2 Residual Uncertainties

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

2. Clinical Pharmacology Studies to Support the Use of a Non-US-licensed Comparator Product

In Study CT-P42 3.1, EU-Eylea was used as the reference comparator product. A 3-way analytical comparison between three products, CT-P42 3.1, US-Eylea and EU-Eylea was used to support the use of EU-Eylea in the Study CT-P42 3.1. In the previous interaction with the Applicant, the Agency agreed in principle that an establishment of a scientific bridge via adequate pairwise comparisons between these three products would support the use of EU-Eylea as a reference comparator product in the planned 351(k) application (Pre-IND 147335 Meeting Minutes dated 07/21/2020). Refer to the review by Office of Product Quality for the adequacy of the analytical bridging to support the use of the EU-Eylea in the phase 3 comparative clinical trial, CT-P42 3.1.

3. CLINICAL PHARMACOLOGY ASSESSMENT

3.1 Clinical Pharmacokinetics

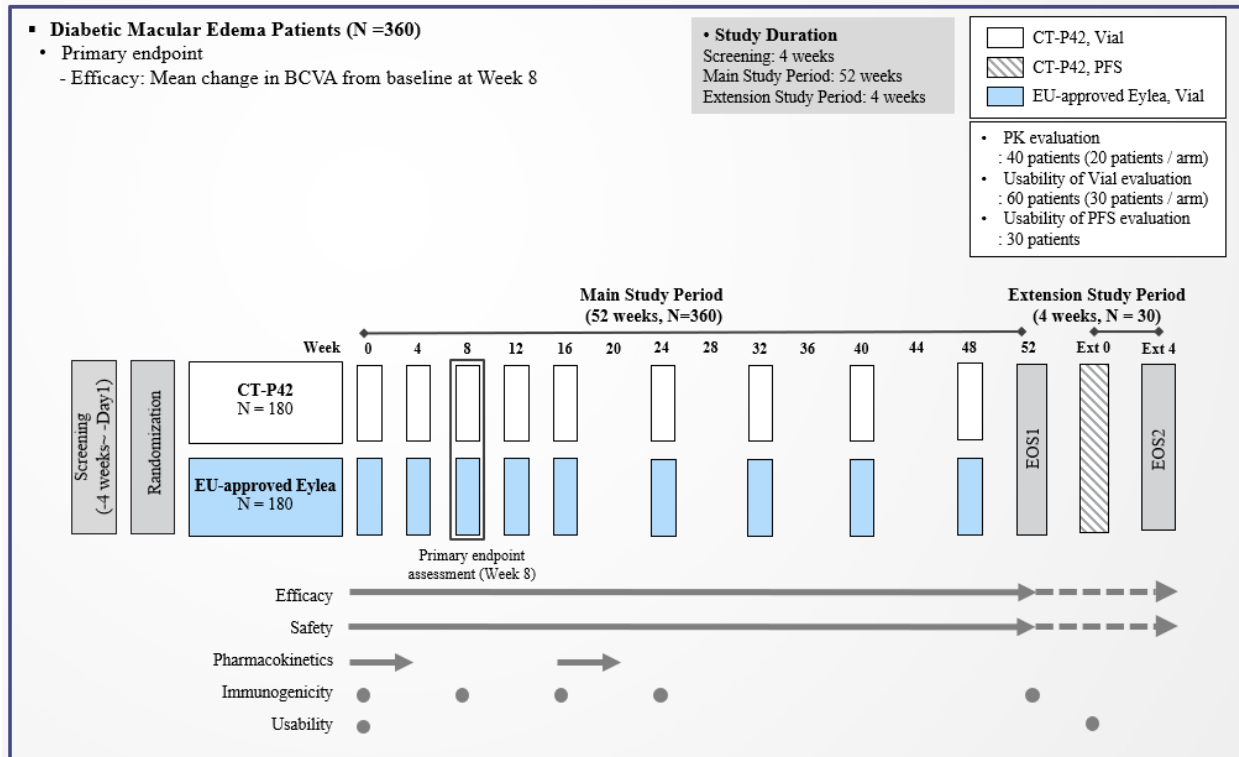
A PK similarity assessment was conducted in a subset of subjects within a pivotal phase 3 comparative clinical trial, CTP in patient population (i.e., subjects with DME). A standalone PK similarity study in healthy subject was not conducted as aflibercept is administered by intravitreal (IVT) injection to treat diseases that are localized to the eye with low systemic exposures and the conduct of a PK study in healthy subjects with IVT injections is considered unethical. The objective of the PK sub-study was to evaluate and descriptively compare the systemic exposure of CT-P42 versus Eylea in subjects participating in the PK evaluation.

Clinical Pharmacology Study Design Features and Endpoints

Study CT-P42 3.1 was a phase 3, multicenter, double-masked, randomized, active-controlled, parallel-group study in subjects with DME. A total of 348 subjects were randomized in a 1:1 ratio to receive either CT-P42 (2 mg/ 0.05 mL) or EU-Eylea (2 mg/ 0.05 mL) in the study eye by IVT using a single-dose vial once every four weeks for 5 doses, then every 8 weeks for 4 doses in the Main Study Period (52 weeks). 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

subjects with DME. A total of 30 subjects entered an Extension Study Period. The study design is illustrated in Figure 1 below.

Figure 1. Study Design of Study CT-P42 3.1



Abbreviations: BCVA, Best Corrected Visual Acuity; EOS, end-of-study; Ext 0, Extension Week 0; Ext 4, Extension Week 4; EU, European Union; N = number of patients; PFS, prefilled syringe; PK, pharmacokinetics.

Note: The figure reflects the number of subjects that were planned, not the actual number of subjects that were evaluated.

Source: CSR CT-P42 3.1 Figure 9-1

A PK sub-study was conducted in 23 subjects. The PK population includes those who received at least 1 full dose of study drug and provided at least one posttreatment PK sample in the Main Study Period. A total of 11 subjects in the CT-P42 group and 12 subjects in the Eylea group were included in the PK analysis. Only one subject (ID (b) (6)) was excluded from the PK population as samples from this subject could not be transferred to the central laboratory due to the War in Ukraine.

PK samples were collected at pre-dose, 24 hours, 48 hours, and 72 hours after both the 1st and the 5th dose. The collected samples were analyzed for free (VEGF-unbound) aflibercept.

Blood samples for immunogenicity assessment were collected prior to study drug administration at Week 0 (Day 1), Week 8, Week 16, Week 24, and Week 52 (end-of-study [EOS]), or when immune-related adverse events (AEs) occurred.

Bioanalytical assay and performance for PK sample analysis

Plasma concentrations of CT-P42 and aflibercept were measured using a validated meso scale discovery (MSD)-electrochemiluminescence (ECL) immunoassay. The lower and upper quantification limits of the assay were 16 ng/mL and 1024 ng/mL, respectively. All PK samples were analyzed within the established stability period of 463 days (i.e., the maximum duration between sample collection and analysis was 322 days). Refer to Appendix for more detailed information regarding the bioanalytical assay validation and performance.

PK of CT-P42 and EU-Eylea in subjects with DME

The descriptive statistics for plasma aflibercept concentrations from the CT-P42 and EU-Eylea groups are presented in Table 1. The PK parameters from the two groups are summarized in Table 2. The graph of plasma concentrations over time is shown in Figure 2. A high inter-subject variability in PK data was observed in both treatment groups with %CV of plasma concentrations ranging from 69.4% to 138.9% (Figure 3). While the mean concentrations in the CT-P42 were numerically higher than the concentrations in EU-Eylea in general, clinical meaningfulness in terms of systemic safety of the observed difference is likely minimal. From a clinical pharmacology perspective, there are no meaningful differences in the systemic exposures that would have any implications on systemic safety following administration of CT-P42 and EU-Eylea in subjects with DME.

Table 1. Plasma Concentrations of Aflibercept

Timepoint Statistic	CT-P42 N=11	EU-Eylea N=12
Week 0, pre-dose		
n	11	11
Mean ± SD	0.00 ± 0.00	0.00 ± 0.00
Geometric Mean	N.C	N.C
%CV	N.C	N.C
Median (Min, Max)	0.00 (0.0, 0.0)	0.00 (0.0, 0.0)
Week 0, 24 hours after dose administration		
n	11	11
Mean ± SD	55.74 ± 42.71	37.97 ± 44.37
Geometric Mean	42.09	26.53
%CV	76.6	116.9

Median (Min, Max)	54.80 (0.0, 153.0)	27.60 (0.0, 156.0)
Week 0, 48 hours after dose administration		
n	11	11
Mean ± SD	58.25 ± 40.40	31.28 ± 32.20
Geometric Mean	45.17	N.C
%CV	69.4	102.9
Median (Min, Max)	55.20 (0.0, 133.0)	27.00 (0.0, 96.7)
Week 0, 72 hours after dose administration		
n	11	11
Mean ± SD	50.92 ± 40.92	22.85 ± 23.48
Geometric Mean	36.57	N.C
%CV	80.4	102.8
Median (Min, Max)	48.40 (0.0, 113.0)	17.90 (0.0, 62.9)
Week 16, pre-dose		
n	8	10
Mean ± SD	6.90 ± 9.58	0.00 ± 0.00
Geometric Mean	N.C	N.C
%CV	138.9	N.C
Median (Min, Max)	0.00 (0.0, 19.7)	0.00 (0.0, 0.0)
Week 16, 24 hours after dose administration		
n	8	10
Mean ± SD	57.18 ± 54.92	51.88 ± 46.47
Geometric Mean	41.30	37.30
%CV	96.1	89.6
Median (Min, Max)	48.85 (0.0, 183.0)	47.30 (0.0, 157.0)
Week 16, 48 hours after dose administration		
n	8	9
Mean ± SD	55.00 ± 43.12	52.91 ± 41.92
Geometric Mean	43.18	39.74
%CV	78.4	79.2
Median (Min, Max)	45.65 (0.0, 147.0)	53.70 (0.0, 140.0)
Week 16, 72 hours after dose administration		
n	8	9
Mean ± SD	52.18 ± 38.55	45.59 ± 25.73
Geometric Mean	40.94	38.57
%CV	73.9	56.4
Median (Min, Max)	50.40 (0.0, 128.0)	59.80 (0.0, 74.0)

Notes: For descriptive statistics, BLQ was treated as zero except for geometric mean. For geometric means, BLQ values were set to 0.5*LLoQ (LLoQ = 16 mcg/L). Geometric mean was only calculated if at least 2/3 of all plasma concentration values were valid and higher than LLoQ for respective time point.

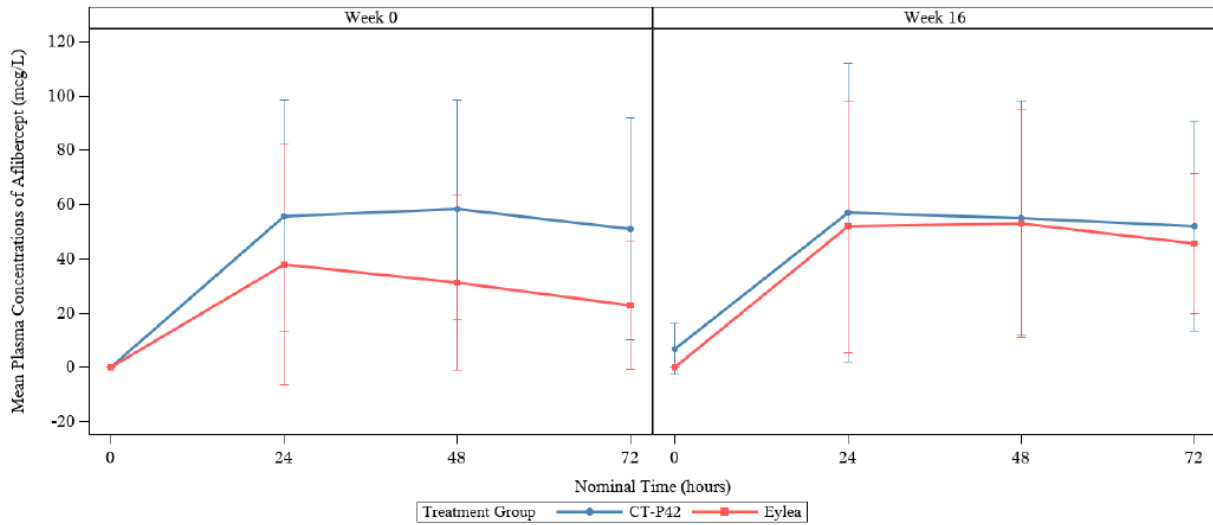
Source: CSR CT-P42 3.1 Post-text Table 14.2.7.1

Table 2. Pharmacokinetic Parameters of Aflibercept

Parameters Statistic	CT-P42 N=11	EU-Eylea N=12
Cmax (mcg/L) After 1st Dose		
n	11	11
Mean ± SD	66.79 ± 42.70	42.93 ± 43.64
Geometric Mean	53.46	30.95
%CV	63.9	101.7
Median (Min, Max)	66.70 (0.0, 153.0)	34.40 (0.0, 156.0)
Cmax (mcg/L) After 5th Dose		
n	8	10
Mean ± SD	64.41 ± 52.49	57.12 ± 46.51
Geometric Mean	49.90	41.56
%CV	81.5	81.4
Median (Min, Max)	53.20 (0.0, 183.0)	58.70 (0.0, 157.0)
Tmax (mcg/L) After 1st Dose		
n	11	11
Mean ± SD	40.7152 ± 22.0180	36.9227 ± 16.3752
Geometric Mean	35.7819	33.9879
%CV	54.1	44.3
Median (Min, Max)	24.0000 (22.333, 72.333)	25.0667 (22.833, 71.667)
Tmax (mcg/L) After 5th Dose		
n	8	10
Mean ± SD	43.9833 ± 23.9879	42.6700 ± 22.4691
Geometric Mean	38.2631	37.5524
%CV	54.5	52.7
Median (Min, Max)	35.0833 (21.667, 71.417)	35.6417 (22.433, 72.833)

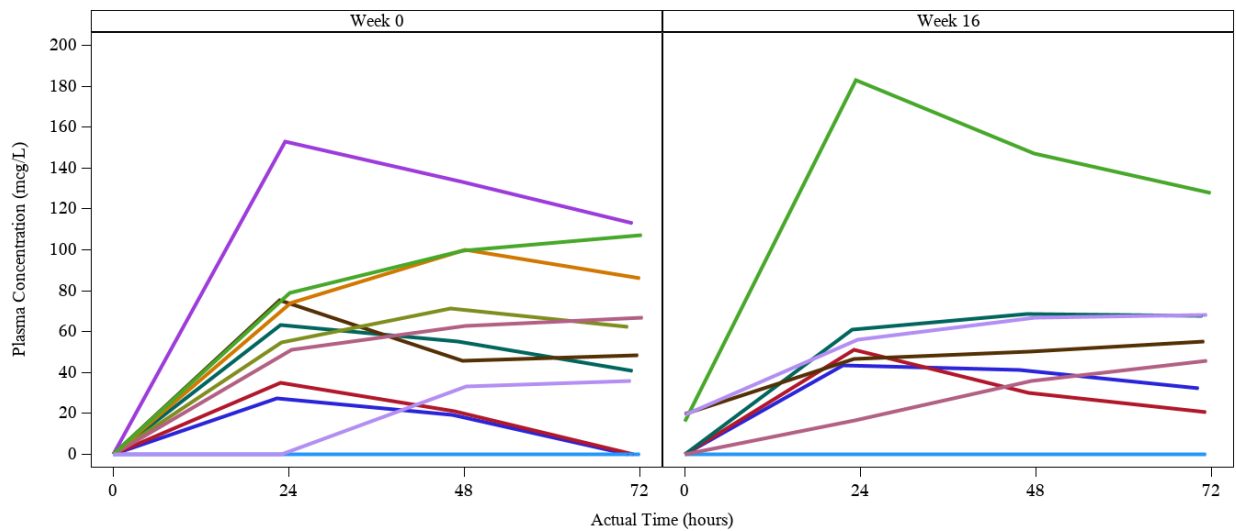
Notes: If Cmax is 0, 0.5 * LLoQ (LLoQ = 16 mcg/L) was used for the calculation of geometric means.
Source: CSR CT-P42 3.1 Post-text Table 14.2.7.3

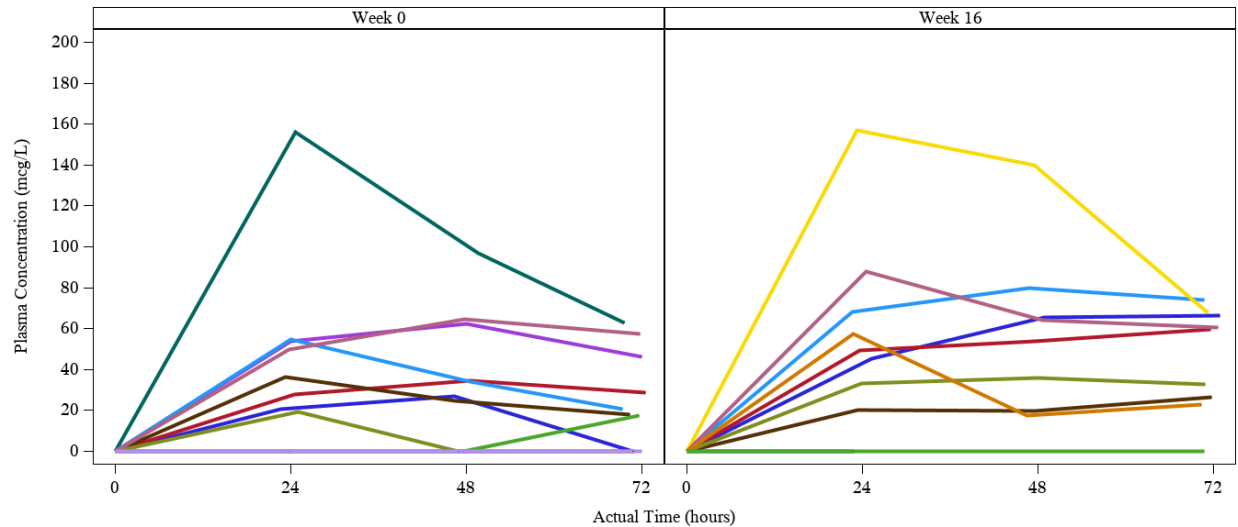
Figure 2. Mean (SD) Pharmacokinetic Plasma Profiles of Aflibercept Following 1st Dose (Week 0) and 5th Dose (Week 16)



Source: CSR CT-P42 3.1 Post-text Table 14.2.7.3

Figure 3. Overlay Plot of Plasma Concentrations of Aflibercept per Individual Subject





Top Panel: CT-P42 Treatment Group; Bottom Panel: EU-Eylea Treatment Group
 Source: CSR CT-P42 3.1 Post-text Figure 14.2.4.6

3.2 Immunogenicity Assessment

Study Design Features of the Immunogenicity Assessment

Immunogenicity (ADA and NAb) was evaluated in all subjects in Study CT-P42 3.1 as one of secondary objectives. Refer to Section 3.1 above for the detailed study design of Study CT-P42 3.1.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation

Samples for immunogenicity assessment were collected prior to study drug administration at Week 0 (Day 1), Week 8, Week 16, Week 24, and Week 52 (EOS), or when immune-related adverse events (AEs) occurred. The sampling timepoints were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation.

Immunogenicity Endpoints

- Incidence of ADA
- Incidence of NAb

Immunogenicity Assays

For determining the presence of ADA and NAb, validated electrochemiluminescence (ECL) assays were employed in 3-tiered steps: 1) ADA screening, 2) ADA confirmatory

assay, 3) ADA titration and estimation of neutralizing activity. Refer to the review by the Office of Biotechnology Products for the adequacy of immunogenicity assays.

Immunogenicity Assessment Results

The immunogenicity results are summarized in Table 3. Overall, the incidence of positive ADA was low in both treatment groups and was comparable between the treatment groups. The incidence of ADA positive after the first study drug administration was 1.7% in both the CT-42 and EU-Eylea treatment groups. The incidence of NAb was also low. Two (1.2%) subjects in the CT-P42 group and 1 (0.6%) subject in the Eylea group showed NAb positive result at post-treatment visit. The ADA titer results up to Week 24 by each visit are summarized in Table 4. All patients with ADA positive results showed low ADA titer. The mean and the median ADA Titer results were generally similar between the two treatment groups at each visit.

Table 3. Summary of Immunogenicity Results

Visit ADA Result NAb Result	CT-P42 N=173	EU-Eylea N=175	Total N=348
At least 1 ADA positive result after the 1 st study drug administration, n (%)	3 (1.7%)	3 (1.7%)	6 (1.7%)
All ADA negative result after the 1st study drug administration, n (%)	167 (96.5%)	170 (97.1%)	337 (96.8%)
Week 0 (prior to study drug administration)			
ADA Positive	3 (1.7%)	2 (1.1%)	5 (1.4%)
NAb Positive	0	0	0
NAb Negative	3 (1.7%)	2 (1.1%)	5 (1.4%)
ADA Negative	163 (94.2%)	171 (97.7%)	334 (96.0%)
Week 8			
ADA Positive	3 (1.7%)	2 (1.1%)	5 (1.4%)
NAb Positive	2 (1.2%)	0	2 (0.6%)
NAb Negative	1 (0.6%)	2 (1.1%)	3 (0.9%)
ADA Negative	164 (94.8%)	164 (93.7%)	328 (94.3%)
Week 16			
ADA Positive	2 (1.2%)	1 (0.6%)	3 (0.9%)
NAb Positive	0	1 (0.6%)	1 (0.3%)
NAb Negative	2 (1.2%)	0	2 (0.6%)
ADA Negative	159 (91.9%)	156 (89.1%)	315 (90.5%)
Week 24			
ADA Positive	2 (1.2%)	2 (1.1%)	4 (1.1%)
NAb Positive	0	0	0
NAb Negative	2 (1.2%)	2 (1.1%)	4 (1.1%)
ADA Negative	160 (92.5%)	156 (89.1%)	316 (90.8%)

Source: CSR CT-P42 3.1 Post-text Table 14.3.6.13

Table 4. ADA Titer Results

Visit	Statistic	CT-P42 N=173	EU-Eylea N=175
Week 0	N	3	2
	Mean (SD)	41.7 (14.4)	50.0 (0.0)
	Median (Min, Max)	50.0 (25, 50)	50.0 (50, 50)
Week 8	N	3	2
	Mean (SD)	50.0 (0.0)	50.0 (0.0)
	Median (Min, Max)	50.0 (50, 50)	50.0 (50, 50)
Week 16	N	2	1
	Mean (SD)	50.0 (0.0)	50.0 (N.C)
	Median (Min, Max)	50.0 (50, 50)	50.0 (50, 50)
Week 24	N	2	2
	Mean (SD)	50.0 (0.0)	50.0 (0.0)
	Median (Min, Max)	50.0 (50, 50)	50.0 (50, 50)

Source: CSR CT-P42 3.1 Post-text Table 14.3.6.14

Impact of Immunogenicity on PK of CT-P42

None of the subjects who participated in the PK sub-study had positive ADA results. Therefore, the impact of immunogenicity on PK could not be assessed.

Impact of Immunogenicity on Efficacy of CT-P42

The mean change from baseline in best corrected visual acuity (BCVA) scores at Week 8, the primary efficacy endpoint in the Study CT-P42 3.1, by ADA status is summarized in Table 5. While the mean change in BCVA scores were numerically higher in the ADA positive groups compared to the ADA negative groups for both CT-P42 and EU-Eylea treatment groups, low ADA incidences and high variability in data prevent from reaching a conclusion regarding the impact of immunogenicity on efficacy.

Table 5. Change from Baseline of BCVA at Week 8 by ADA Status

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

Source: CSR CT-P42 3.1 Post-text Table 14.2.1.2a

Impact of Immunogenicity on Safety of CT-P42

There was a total of 6 subjects who were tested ADA positive after drug administration in the study. Among those 6 subjects, 3 subjects experienced at least 1 treatment-emergent adverse event (TEAE); however, none of these TEAEs were study-drug related. As the incidence of ADA positive was very low, the impact of immunogenicity on safety cannot be meaningfully assessed.

4. Appendix

Summary of Bioanalytical Method Validation and Performance

The PK samples obtained from Study CT-P42 3.1 were analyzed using a validated ECL immunoassay. The method validation and bioanalysis performance are summarized in Table 6 and Table 7, respectively.

Table 6. Validation Summary of a Bioanalytical Method for the Quantification of CT-P42 and Aflibercept in Plasma

Report ID	RQXO2, RXQO3 (Addendum 1), RQXO5 (Addendum 2)	
Bioanalytical Methodology	ECL immunoassay	
Matrix	Human plasma	
Anticoagulant	CTAD	
Assay Range	16 to 1024 ng/mL	
Minimum Required Dilution (MRD)	1:40 in assay buffer (PBS containing 1% BSA and 0.05% Tween-20)	
Precision (%CV)	CT-P42	EU-Eylea
Standards	2.97 to 19.0	N/A
Intra-assay LLOQ/ULOQ	5.75/3.23	8.14/4.09
Inter-assay LLOQ/ULOQ	11.0/12.9	11.1/10.2
Intra-assay LQC/MQC/HQC	4.45/5.08/3.42	4.97/4.04/6.92
Inter-assay LQC/MQC/HQC	7.77/8.52/6.10	6.78/8.74/7.74
Accuracy (%DFT)	CT-P42	EU-Eylea
Standards	-3.97 to 1.94	N/A
LLOQ/ULOQ	9.51/3.42	8.52/3.51
LQC/MQC/HQC	11.2/3.81/7.63	7.55/4.79/4.82
Freeze/thaw Stability (Freeze at -80 °C and thaw at RT Cycle) after 6 cycles	Stable up to 6 cycles of freeze/thaw at LQC and HQC	
Thawed Matrix Stability at RT for 24 hours	Stable at RT for 24 hours at LQC and HQC	
Long-term Frozen Matrix Stability at -25 °C for 463 Days	Stable at -25 °C for 463 days at LQC and HQC	
Long-term Frozen Matrix Stability at -80 °C for 463 Days	Stable at -80 °C for 463 days at LQC and HQC	
Selectivity	Met the predefined acceptance criteria: <ul style="list-style-type: none"> • $\geq 80\%$ of blank samples must quantitate $< \text{LLOQ}$ • $\geq 80\%$ of fortified samples must quantitate within $\pm 20.0\%$ at high level and $\pm 25.0\%$ at LLOQ of theoretical 	
Specificity (Hemolysis & Lipemia)	Met the predefined acceptance criteria: <ul style="list-style-type: none"> • $< \text{LLOQ}$ for blank hemolyzed or lipemic samples 	

	<ul style="list-style-type: none"> • %CV ≤ 20.0% • % DFT ± 20.0% for fortified hemolyzed or lipemic samples (± 25.0% at the LLOQ)
Prozone or Hook effect	No prozone or hook effect observed up to 40,000 ng/mL
Dilutional Linearity up to 1024-fold	The accurate measurement of concentrations for the diluted samples was validated within the quantitative assay range.
Dilutional Parallelism	The precision (%CV) between diluted samples were ≤ 30.0% at 5 out of 5 samples (100.0%)

Source: RQX02, RQX03, RQX05, Module 2.7.1

Table 7. Bioanalysis Performance Summary

Bioanalytical Report	RRYK
Sample matrix	Human plasma
Total samples	Of the 166 original and 161 duplicate samples received by the bioanalysis lab, a total of 165 samples were analyzed in 9 runs.
Calibration standards	%CV ranged from 1.91 to 5.56. %difference from theoretical value ranged from -2.59 to 5.05.
QC performance	%CV: 9.92 (low), 8.77 (mid), 8.29 (high) %difference from theoretical value ranged from -4.41 to -0.168.
Incurred sample reanalysis	Incurred sample re-analysis was performed in a 10.3% of samples; 88.2% of samples passed the predefined reproducibility criteria (± 30.0%) of the initial result.
Study sample analysis/stability	Samples were stored for a maximum of 322 days which is within the established long-term stability period of 463 days.

Source: RRYK

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: BLA 761377
Supplement #: NA
Drug Name: CT-P42, Proposed biosimilar of aflibercept
Indication(s): Neovascular (Wet) Age-Related Macular Degeneration (AMD),
Macular Edema Following Retinal Vein Occlusion (RVO),
Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR)
Applicant: CELLTRION, Inc.
Date(s): Date Submitted: June 29, 2023
Primary Review Due Date: February 29, 2024
BsUFA Goal Date: June 29, 2024
Review Priority: Standard
Biometrics Division: Division of Biometrics VIII
Statistical Reviewer: Sungwoo Choi, Ph.D., DB VIII
Concurring Reviewers: Jessica Kim, Ph.D., DB VIII
Medical Division: Division of Ophthalmology
Clinical Team: Rhea Lloyd, MD, Medical Officer
Project Manager: Dheera Semidey

Keywords: Biosimilar, Best Corrected Visual Acuity

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1 EXECUTIVE SUMMARY

The Applicant (CELLTRION, Inc.) submitted Biologic License Application (BLA) 761377 to demonstrate similarity of the proposed biosimilar product CT-P42 to US-licensed Eylea (afibercept), based on the totality of evidence from the analytical, nonclinical, and clinical data. The clinical program includes, CT-P42 3.1 clinical comparative efficacy and safety study in patients with diabetic macular edema (DME). The study CT-P42 3.1 was a multi-center, randomized, double-masked, active-controlled, parallel group, comparative Phase 3 clinical study with a duration of 60 weeks to evaluate the similarity of CT-P42 and Eylea.

Subjects who met all eligibility criteria were randomized into one of the two treatment groups in a 1:1 ratio to CT-P42 arm or Eylea arm. Randomization was stratified by baseline BCVA (ETDRS Letter Scores < 55 vs. ≥ 55), country, and pharmacokinetic (PK) subgroup (Yes vs. No). A total of 348 subjects were randomized to CT-P42 arm (N = 173) or Eylea arm (N = 175).

The primary efficacy endpoint was the change in BCVA using the ETDRS chart from baseline to Week 8. The primary efficacy analysis was conducted to assess whether there is any clinically meaningful difference between CT-P42 and Eylea in the primary efficacy endpoint based on both full analyses set (FAS) and per-protocol (PP) analysis set. The pre-specified similarity margin was set as [-3, 3] letters.

In terms of the primary efficacy endpoint, the adjusted mean changes in BCVA from baseline at Week 8 were comparable between the two treatment groups with 8.90 letters for CT-P42 and 8.33 letters of Eylea using FAS (8.51 letters for CT-P42 and 8.17 letters for Eylea using PP set). In addition, the adjusted mean differences were 0.568 letters and 0.346 letters with 90% CIs of (-0.528, 1.660) letters and (-0.729, 1.420) using FAS and PP set, respectively, which were contained within the pre-specified similarity margin [-3, 3]. Thus, the study demonstrated the similarity of CT-P42 and Eylea for the primary endpoint in both FAS and PP set.

In summary, the reviewer concludes that this application provides adequate statistical evidence that there is no clinically meaningful difference between CT-P42 and Eylea in the primary efficacy endpoint according to the prespecified biosimilar margin.

2 INTRODUCTION

This section provides an overview of the application, a summary of the clinical studies, and information on data sources submitted in BLA 761377.

2.1 Overview

The Applicant seeks approval of CT-P42 as a proposed biosimilar to US-licensed Eylea (aflibercept). The proposed indication and usage for CT-P42 are identical to those of Eylea.

Eylea was approved for the following treatments in the United States (US) of the following:

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

The Applicant selected DME as the study indication among all approved indications, and conducted one phase 3 clinical study, CT-P42 3.1, which is hereafter referred to as Study 4231, to evaluate the clinical similarity of CT-P42 and Eylea regarding efficacy and safety in the treatment of subjects with DME. Table 1 shows the summary of Study 4231.

Table 1: Summary of specific study reviewed

Study ID	Design	Duration	Treatment / Sample Size	Study Population
CT-P42 3.1	Multi-center, randomized, double masked, active controlled, parallel group, comparative study	Screening: 4 weeks, main study: 52 weeks, and extension study: 4 weeks	CT-P42 2 mg / 180 Eylea 2 mg / 180	Subjects with DME

Source: reviewer's summary based on the clinical study report.

2.2 Data Sources

The data sources for this review include protocol, statistical analysis plans (SAP), clinical study report (CSR), and the datasets.

The protocol, SAP and CSR can be found at the following location:

- <\\CDSESUB1\evsprod\BLA761377\0001\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\diabetic-macular-edema\5351-stud-rep-contr\cltp4231dme>.

The datasets were submitted in the formats of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) in electronic submission. The datasets can be located at

- <\\CDSESUB1\evsprod\BLA761377\0001\m5\datasets\cltp4231dme>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major issues were identified regarding the quality and integrity of the submitted SDTM and ADaM datasets under BLA 761377. The data quality control/assurance procedures are properly documented in the CSRs. The Applicant's primary efficacy results are reproducible using the ADaM datasets.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of Study 4231.

3.2.1 Study Design and Endpoints

Study design

Study 4231 was a multi-center, randomized, double-masked, active-controlled, parallel group, comparative Phase 3 clinical study to demonstrate that there is no clinically meaningful difference between CT-P42 and EU-licensed Eylea in subjects with diabetic macular edema (DME).

The primary objective of Study 4231 was to demonstrate the similarity of CT-P42 and Eylea over 8 weeks, as assessed by change from baseline to Week 8 in best corrected visual acuity (BCVA) using the early treatment of diabetic retinopathy study (ETDRS).

This study was conducted in 83 centers in Czech, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Russia, Slovakia, Spain, Ukraine, Republic of Korea, and India. The number of study centers in the geographical regions are as follows:

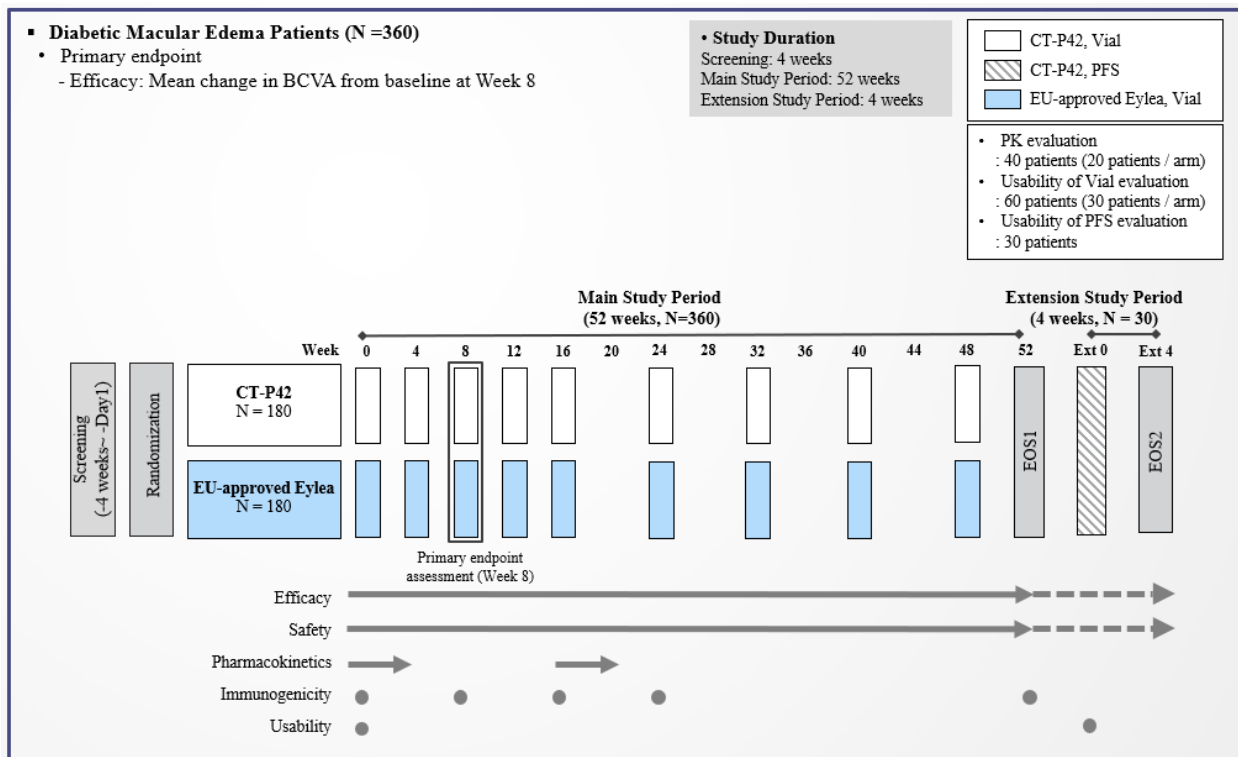
- Czechia (6 centers), Estonia (2 centers), Hungary (7 centers), India (22 centers), Latvia (2 centers), Lithuania (1 center), Poland (11 centers), Republic of Korea (7 centers), Russia (2), Slovakia (4 centers), Spain (7 centers), and Ukraine (3 centers).

The randomization was stratified by:

- Baseline BCVA (ETDRS Letter Scores < 55 vs. \geq 55),
- Country, and
- Pharmacokinetic (PK) subgroup (Yes vs. No).

The study consists of 3 periods: a screening period of 4 weeks, a main study period of 52 weeks, and an extension study period of 4 weeks. During the main study period, a total of 348 subjects were randomized in a 1:1 ratio to CT-P42 arm (N = 173) or Eylea arm (N = 175). The schedule of activities is presented in Figure 1. During the study, subjects received either CT-P42 or Eylea via intravitreal (IVT) injection with a single-dose vial at 4-week intervals for the initial 5 doses, followed by a transition to 8-week interval for the subsequent 4 doses (baseline, Week 4, Week 8, Week 12, Week 16, Week 24, Week 32, Week 40, and Week 48). The Week 8 assessment corresponds to the primary endpoint evaluation time.

Figure 1: Schematic of the study design



BCVA: Best Corrected Visual Acuity, EOS: end-of-study, Ext 0: Extension Week 0, Ext 4: Extension Week 4, EU: European Union, PFS: prefilled syringe

Source: Figure 9-1 of the Clinical Study Report (CSR)

Reviewer's comments: We note that in the Table 9-2 of CSR and study data file, there is a visit at Week 1 that does not involve the administration of the study drug.

Study endpoints

The primary efficacy endpoint was the change in BCVA using the ETDRS chart from baseline to Week 8. Table 2 summarizes the efficacy endpoints in the Study 4231.

Table 2: Efficacy endpoints in Study 4231

Primary	<ul style="list-style-type: none"> • Change in BCVA using the ETDRS chart from baseline to Week 8
Secondary (Descriptive statistics)	<p>(S1) Change in BCVA using the ETDRS chart from baseline</p> <p>(S2) Change in central subfield thickness (CST) from baseline as determined by spectral-domain Optical Coherence Tomography (OCT)</p> <p>(S3) Subjects who gained ≥ 5, ≥ 10, and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS</p> <p>(S4) Subjects who lost ≥ 5, ≥ 10, and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS</p> <p>(S5) Patients with ≥ 2-step improvement from baseline in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score as assessed by fundus photography (FP)</p>

3.2.2 Statistical Methodologies

In this section we primarily focus on describing statistical methodologies for analyzing the primary efficacy endpoint. Hypothesis testing was conducted only for the primary endpoint, and no formal analysis based on statistical hypothesis was intended for the other endpoints.

Analysis populations

The SAP defines the following analysis sets:

- The intention-to-treat (ITT) set includes all subjects who were randomly assigned to receive either of the study drugs (CT-P42 or Eylea), regardless of whether any study drug was administered.
- Safety set for main study period includes all randomized subjects who received at least one full or partial dose of study drug in the main study period.
- The full analysis set (FAS) includes all randomized subjects who receive at least one full dose of study drug during the main study period. The FAS is the primary analysis set for efficacy endpoint analyses.
- The per-protocol (PP) set includes all randomized subjects who received all full doses of study drug up to Week 4 (total 2 injections), had a BCVA assessment at Week 8, and had no major protocol deviations which may affect the interpretation of study results of primary efficacy endpoint. Supportive analyses for the efficacy analyses are performed on the PP analysis set.
 - Major protocol deviations:
 1. Significant GCP non-compliance,
 2. Mis-randomization up to Week 4,
 3. Non-adherence to inclusion/exclusion criteria which affected primary efficacy result,
 4. Receipt of prohibited therapy which affected primary efficacy result.

Note that study patients were analyzed based on the treatment to which they were randomly assigned.

Sample size determination

The sample size calculation was based on the following assumptions:

- Similarity margin of [-3, 3] letters
- No expected mean difference between two treatment groups
- Standard deviation (SD) of 8.2 letters
- 89% power
- 90% two-sided confidence interval (significance level of 5%)

With the assumptions, a sample size of 158 subjects per study group (316 subjects in total) was required to achieve a desired power of 89%. After considering 12% dropouts, a total of 360 subjects was planned for the study.

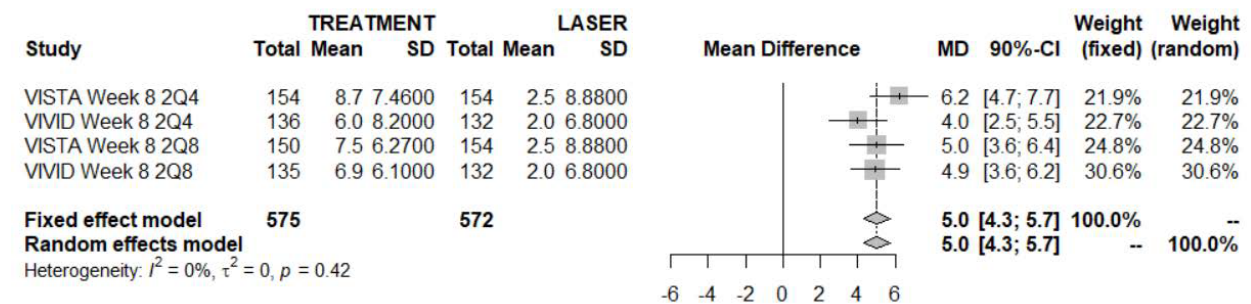
Reviewer’s comments: The reviewer confirmed that 8.2 of the assumed standard deviation originated from a pooled standard deviation derived in the study VISTA Week 8 2Q4, which was one of the studies used in the derivation of the similarity margin (See Pages 27-28, 4.3 of Clinical Overview). The study size of 316 was reproducible using the listed assumptions.

Similarity margin justification

The determination of the similarity margin for the difference in mean change from baseline in BCVA relied on the data from two randomized controlled studies conducted on the reference product (VIVID/VISTA [Brown et al., 2015]). These studies compared the efficacy of Eylea with laser therapy in patients diagnosed with DME.

The similarity margin of ± 3 letters were determined from the findings of the meta-analysis, which identified the lower limit of the 90% confidence interval (CI) as 4.3 letters (refer to Figure 2). This chosen margin of ± 3 maintains a conservative estimate of approximately 30% of the reference product treatment effect compared to laser therapy, based on this calculated estimate.

Figure 2: Meta-analysis of the VIVID and VISTA Studies



Source: Figure 2.5-3 of the Clinical Overview

Analysis of primary endpoint

The hypotheses to be tested are

$$H_0: |\mu_C - \mu_E| \geq 3 \quad \text{versus} \quad H_A: |\mu_C - \mu_E| < 3,$$

where μ_C and μ_E are the mean change from baseline to week 8 in BCVA for CT-P42 and Eylea, respectively; a similarity margin of ± 3 letters are used. To establish the similarity between CT-P42 and Eylea, the 90% confidence interval (CI) for the mean difference $\mu_C - \mu_E$ was calculated. The null hypothesis H_0 is rejected with a type I error probability $\alpha = 0.05$ if the 90% CI for $\mu_C - \mu_E$ is contained within the interval $[-3, 3]$. Rejecting the null hypothesis H_0 supports the conclusion of similarity between CT-P42 and Eylea.

The 90% CI for the mean difference $\mu_C - \mu_E$ was constructed using the least-squares mean and error estimates derived from an Analysis of Covariance (ANCOVA). The ANCOVA includes the baseline BCVA and country as covariates, and treatment as a factor only for study eye (Detailed criteria for selection of the study eye are described in 9.3 of CSR).

Reviewer's comments: The reviewer included all the stratified randomization factors, including PK subgroup into the ANCOVA model.

Handling of missing data

Missing data was not imputed in the primary analysis of the primary endpoint. To assess the impact of missing data on the primary efficacy endpoint results, additional analyses with missing data imputation were conducted (See the sensitivity analysis section). Table 3 presents the number of subjects who had missing BCVA assessments at Week 8 for the primary efficacy analysis.

Table 3: Summary of subjects with missing BCVA data at Week 8 for the primary endpoint

	CT-P42	Eylea	Overall
	N = 173	N = 175	N = 348
Subjects with missing BCVA at Week 8	4 (2.3%)	3 (1.7%)	7 (2.0%)

Source: reviewer's summary based on the clinical study report.

Sensitivity analysis for the primary endpoint

To assess the impact of missing data on the primary endpoint results, multiple imputation (MI) under the assumption of missing at random (MAR) is applied. All subjects with non-missing baseline BCVA score in FAS is included in the analysis. To create the imputed datasets, linear regression model with baseline BCVA score, country, and treatment group as covariates is used. Covariates with missing values are excluded from the imputation process. The results from each imputed dataset are pooled using MIANALYZE procedure in SAS.

The reviewer also conducted the following additional sensitivity analysis:

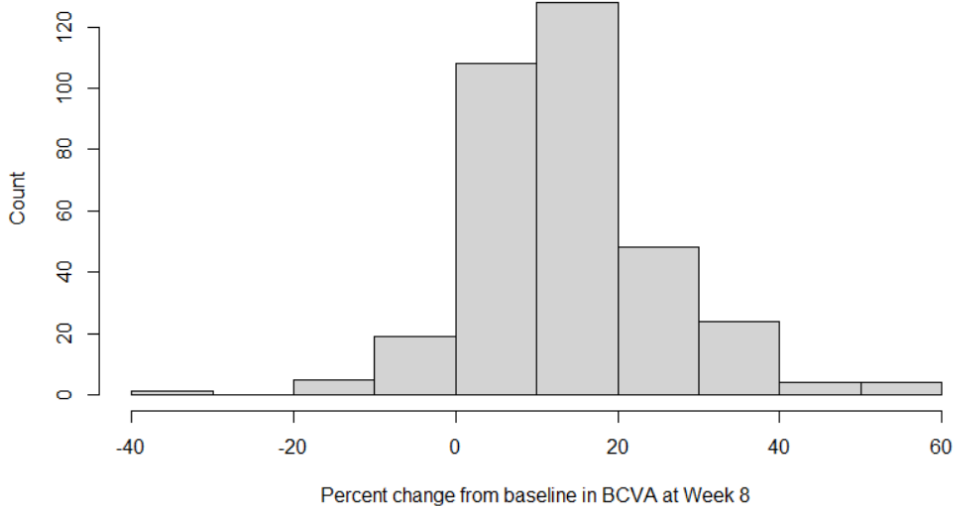
- Analysis of the primary endpoint using mixed model for repeated measurements (MMRM) model
- Analysis of the primary endpoint in which missing BCVA values at Week 8 were replaced using a conservative approach (34% reduction in BCVA from baseline for CT-P42 group, and 57% increase in BCVA baseline for Eylea group)

Reviewer's comments: The assumptions for the FDA's conservative approach were based on the distribution of the individual subjects' percent change from baseline in BCVA in Week 8,

$$\frac{\text{Week 8} - \text{Baseline}}{\text{Baseline}} \times 100,$$

as the minimum and maximum values of the percent change from baseline were -34% and 57%, respectively (refer to Figure 3).

Figure 3: Histogram of percent change from baseline in BCVA at Week 8



Source: Reviewer's analysis

Analysis of secondary endpoints

Recall that the other secondary endpoints were

- Change in BCVA using the ETDRS chart from baseline
- Change in CST from baseline as determined by spectral-domain OCT
- Subjects who gained ≥ 5 , ≥ 10 , and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS

- Subjects who lost ≥ 5 , ≥ 10 , and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS
- Patients with ≥ 2 -step improvement from baseline in the ETDRS DRSS score as assessed by FP.

The mean changes in BCVA and CST from baseline are summarized using time trend figures of descriptive statistics. The proportions of patients who gained/lost ≥ 5 , ≥ 10 , and ≥ 15 ETDRS letters from baseline in BCVA are summarized using bar plots by treatment group and each scheduled visit of main study period. Percentage of patients with a ≥ 2 -step improvement from baseline in the ETDRS DRSS score is also be summarized using frequency tables by treatment group and visit. No formal hypothesis testing was planned for other secondary endpoints.

Subgroup analysis

The primary endpoint was analyzed across the subgroups defined by the following factors:

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

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis populations, subject disposition and primary reasons for study discontinuation are summarized in Table 4. A total of 348 subjects were randomized in two groups: 173 subjects in CT-P42 and 175 subjects in Eylea. Of the randomized subjects (ITT analysis set), 16 subjects were excluded from the PP analysis set.

A total of 13 subjects (3.7%) discontinued from the study on or before Week 24, 5 subjects from CT-P24 group and 8 subjects from Eylea groups. The most common reasons for discontinuation from the study among all randomized subjects were withdrawal of consent (1.4%) and adverse event (1.1%).

Table 4: Analysis population and subject disposition

	CT-P42	Eylea	Overall
Screened			484
Screening failure			136
Randomized (ITT)	173 (100.0)	175 (100.0)	348 (100.0)
Safety	173 (100.0)	175 (100.0)	348 (100.0)
FAS	173 (100.0)	175 (100.0)	348 (100.0)
PP	165 (95.4)	167 (95.4)	332 (95.4)
Excluded from PP ¹	8 (4.6)	8 (4.6)	16 (4.6)
Major protocol deviation	3 (1.7)	4 (2.3)	7 (2.0)
Did not receive study drug at Week 4	2 (1.2)	3 (1.7)	5 (1.4)
No BCVA assessment at Week 8	4 (2.3)	3 (1.7)	7 (2.0)
Completed Week 24	168 (97.1)	167 (95.4)	335 (96.3)
Discontinued up to Week 24	5 (2.9)	8 (4.6)	13 (3.7)
Withdrew consent	2 (1.2)	3 (1.7)	5 (1.4)
Adverse event	2 (1.2)	2 (1.1)	4 (1.1)
Withdrawn by investigator	0 (0.0)	1 (0.6)	1 (0.3)
Lost to follow-up	1 (0.6)	1 (0.6)	2 (0.6)
Protocol deviation	0 (0.0)	1 (0.6)	1 (0.3)

¹ Subjects were counted once within each reason. The total number of exclusions may add up to more than this number of subjects excluded from PP population because a subject may have multiple reasons for exclusion. Source: This table was produced by the reviewer using Tables 10-1 and 11-2 of CSR for Study 4231.

Demographic, and stratification details are summarized in Table 5. The average age was 62.7 years of age (range 25 to 86 years of age). A total of 203 patients, constituting 58.3% of the sample, were male. Among the female patients, the majority were deemed not to be of childbearing potential. Most patients were white, constituting 224 individuals (64.4% of the total), and identified as non-Hispanic or non-Latino, accounting for 331 individuals (95.1% of the total). A significant proportion of patients exhibited a baseline HbA1c level of $\leq 8\%$, encompassing 229 patients (65.8% of the total), while the majority identified as never-smokers, comprising 245 patients (70.4% of the total).

Most patients were enrolled in India, with a total of 104 (29.9%) patients. At baseline, most patients had a BCVA score of ≥ 55 letters, comprising 253 (72.7%) patients in total. Overall, the proportions of patients in the PK subgroup were well-balanced between the two treatment groups, with 12 (6.9%) patients in the CT-P42 group and 12 (6.9%) patients in the Eylea group.

In general, the demographic, and stratification details were comparable between the two treatment groups.

Table 5: Demographics and stratification details (ITT analysis set)

	CT-P42	Eylea	Overall
ITT analysis set	N = 173	N = 175	N = 348
Demographics			
Age (years)			
Mean (SD)	62.5 (9.6)	62.9 (10.3)	62.7 (10.0)
Median	63.0	63.0	63.0
Min, Max	32, 85	25, 86	25, 86
Female fertility status, 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)
Gender, n (%)			
Male	106 (61.3)	97 (55.4)	203 (58.3)
Female	67 (38.7)	78 (44.6)	145 (41.7)
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)
Race, n (%)			
Asian	61 (35.3)	63 (36.0)	124 (35.6)
White	112 (64.7)	112 (64.0)	224 (64.4)
Ethnicity, n (%)			
Hispanic/Latino	5 (2.9)	5 (2.9)	10 (2.9)
Not Hispanic/Latino	166 (96.0)	165 (94.3)	331 (95.1)
Unknown	2 (1.2)	5 (2.9)	7 (2)
Screening value of height (cm)			
Mean (SD)	165.9 (9.7)	166.6 (9.2)	166.3 (9.4)
Median	164.0	167.0	166.5
Min, Max	145.0, 197.0	145.0, 190.0	145.0, 197.0
Screening value of weight (kg)			
Mean (SD)	78.3 (19.3)	76.9 (15.8)	77.6 (17.6)
Median	75.0	75.0	75.0
Min, Max	39.3, 147.0	44.0, 126.0	39.3, 147.0
Baseline HbA1c², 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 (0.0)	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)

Source: This table was produced by the reviewer using the Table 11-3 of CSR for Study 4231.

3.2.4 Results and Conclusions

This section provides efficacy results of the primary, secondary endpoints in Study 4231.

3.2.4.1 Primary Efficacy Endpoint

The objective of the primary efficacy analysis was to demonstrate the similarity of CT-P42 and Eylea in the primary endpoint: change in BCVA using the ETDRS chart from baseline to Week 8 with a similarity margin of ± 3 letters.

Table 6 presents the primary efficacy analysis results.

Table 6: Primary analysis results for mean change in BCVA from baseline to Week 8 (FAS and PP set)

FAS	CT-P42 (N = 173)	Eylea (N = 175)
Baseline BCVA		
n	173	175
Mean (SD)	60.3 (9.7)	60.4 (10.1)
Median (Range)	62.0 (34, 73)	62.0 (34, 73)
BCVA at Week 8		
n	169	172
Mean (SD)	69.1 (11.8)	68.5 (11.1)
Median (Range)	72.0 (32, 92)	70.5 (34, 93)
Change from Baseline to Week 8		
Mean (SD)	8.6 (6.2)	8.0 (6.3)
Median (Range)	8.0 (-7, 27)	7.0 (-18, 25)
Adjusted change from Baseline to Week 8 ^[1]		
LS mean (SE)	8.90 (0.999)	8.33 (0.973)
LS mean difference (SE)		0.568 (0.664)
90% CI for the mean difference		(-0.528, 1.660)
Adjusted change from Baseline to Week 8 ^[2]		
LS mean (SE)	9.43 (0.798)	8.85 (0.775)
LS mean difference (SE)		0.578 (0.664)
90% CI for the mean difference		(-0.517, 1.670)
PP set		
CT-P42 (N = 165) Eylea (N = 167)		
Baseline BCVA		
n	165	167
Mean (SD)	60.5 (9.6)	60.6 (10.1)
Median (Range)	63.0 (34, 73)	62.0 (34, 73)
BCVA at Week 8		
n	165	167
Mean (SD)	69.1 (11.8)	68.8 (10.7)
Median (Range)	72.0 (32, 92)	71.0 (37, 93)
Change from Baseline to Week 8		
Mean (SD)	8.6 (6.3)	8.2 (5.8)
Median (Range)	8.0 (-7, 27)	7.0 (-9, 25)
Adjusted change from Baseline to Week 8 ^[1]		
LS mean (SE)	8.51 (1.040)	8.17 (1.020)
LS mean difference (SE)		0.346 (0.651)
90% CI for the mean difference		(-0.729, 1.420)
Adjusted change from Baseline to Week 8 ^[2]		
LS mean (SE)	9.22 (0.837)	8.84 (0.840)
LS mean difference (SE)		0.377 (0.651)
90% CI for the mean difference		(-0.696, 1.450)

^[1] The reviewer's method. ANCOVA with treatment as a factor, and baseline BCVA, country, and PK subgroup as covariates.

^[2] The applicant's method. ANCOVA with treatment as a factor, and baseline BCVA and country as covariates.

Source: Reviewer's analysis

As shown in Table 6, the adjusted mean changes in BCVA were comparable for the two treatment groups (8.90 letters for CT-P42 and 8.33 letters for Eylea for FAS; 8.51 letters for CT-P42 and 8.17 letters for Eylea for PP set). In addition, the mean differences were 0.568 letters and 0.346 letters with 90% CIs of (-0.528, 1.660) and (-0.729, 1.420) letters for FAS and PP set, respectively, which were contained within the similarity margin of [-3, 3] letters. Thus, the similarity was demonstrated for the primary endpoint.

Reviewer’s comments:

- *The reviewer and the applicant arrived at the same conclusion despite differences in their analyses. The reviewer incorporated the PK subgroup into the ANCOVA model, whereas the applicant’s analysis omitted this factor.*
- *The complete set of the FAS was not employed in the applicant’s analysis due to missing values at Week 8. Furthermore, the ANCOVA model did not incorporate any imputations.*

Sensitivity analysis

The study evaluated robustness of the primary analysis results by conducting different sensitivity analyses. Table 7 shows the summary of sensitivity analysis results. As shown in Table 7, the sensitivity analysis results were consistent with the primary analysis results, leading to the same conclusion for a robust interpretation of the similarity finding.

Table 7: Sensitivity analyses for the primary efficacy endpoint

Analysis Population	Method	LS Mean (SE)		Difference (CT-P42 - Eylea)	
		CT-P42 (N = 173)	Eylea (N = 175)	Mean (SE)	90% CI
FAS	MI with the MAR assumptions ^[1]	9.44 (0.799)	8.84 (0.775)	0.60 (0.663)	(-0.49, 1.69)
FAS	MMRM ^[2]	9.36 (0.725)	8.76 (0.721)	0.60 (0.638)	(-0.45, 1.65)
FAS	ANCOVA using a conservative approach ^[3]	9.67 (1.320)	9.82 (1.280)	-0.151 (1.090)	(-1.95, 1.65)

^[1] The applicant’s method

^[2] The reviewer’s method. MMRM with treatment, visit, treatment-by-visit interaction, and country as fixed effects and baseline BCVA as a covariate.

^[3] The reviewer’s method. Missing data was imputed using a conservative approach as described in “Sensitivity analysis for the primary endpoint” section.

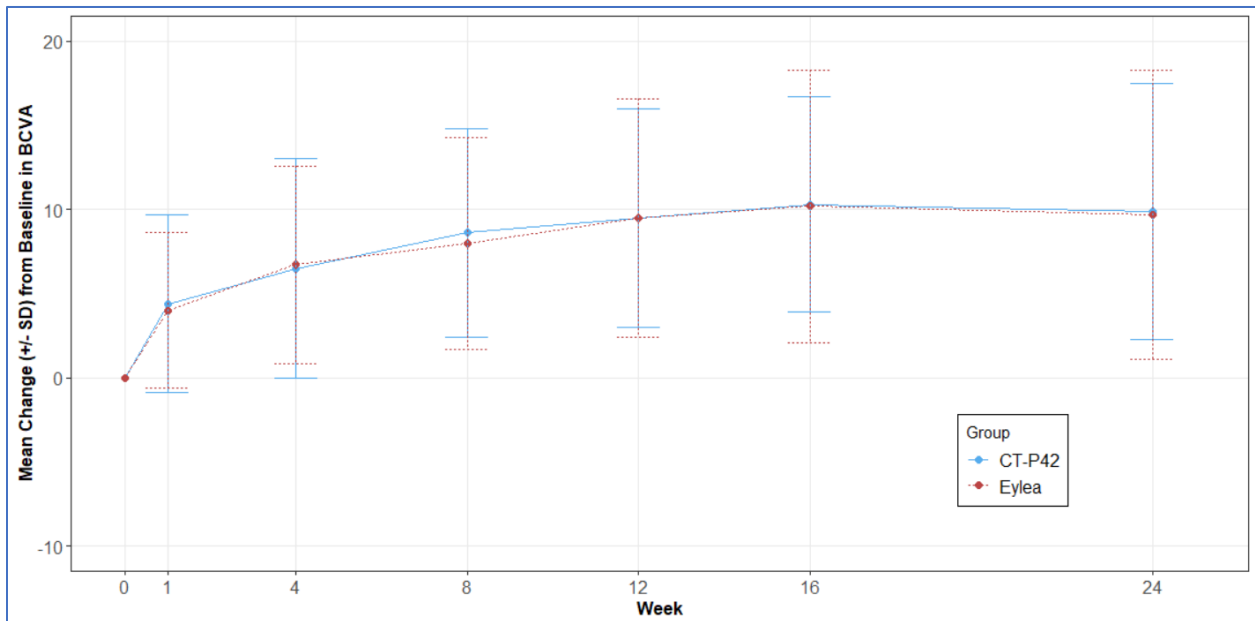
Source: Reviewer’s analysis

3.2.4.2 Secondary Efficacy Endpoints

Change in BCVA using the ETDRS chart from baseline

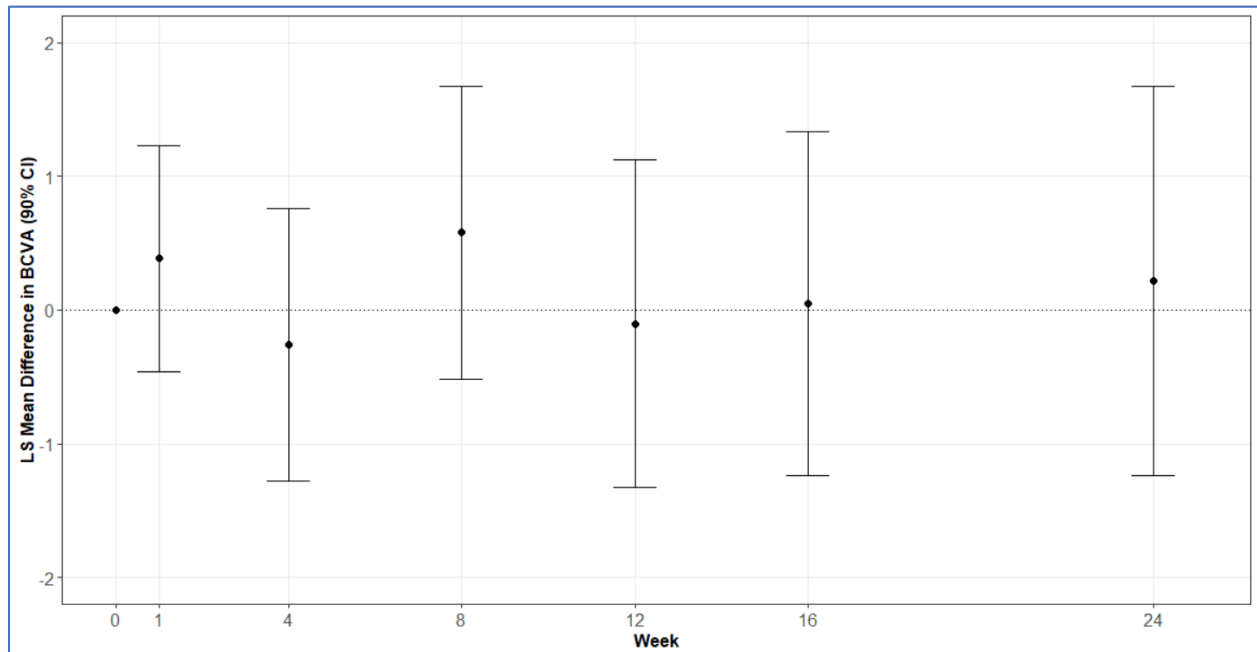
Figures 4 and 5 present the analysis results of the mean change in BCVA over time up to Week 24. Figure 4 displays the mean changes of CT-P42 and Eylea in BCVA over time up to Week 24. Figure 5 shows a noticeable trend of increasing mean changes from baseline in BCVA up to Week 16, followed by a consistent and stable mean change at Week 24. Also, it seems that the time trend lines for CT-P42 and Eylea closely overlap for BCVA. Figure 4 shows the difference (CT-P42 – Eylea) in adjusted mean change in BCVA from baseline over time up to week 24 with 90% CIs. It is seen from Figure 5 that all 90% CIs are contained within the similarity margin of [-3, 3] letters.

Figure 4: Plot for mean change from baseline in BCVA over time up to Week 24 (FAS)



Source: Reviewer's analysis

Figure 5: Plot for difference (CT-P42 – Eylea) in mean change from baseline in BCVA with 90% CI over time up to Week 24 (FAS)

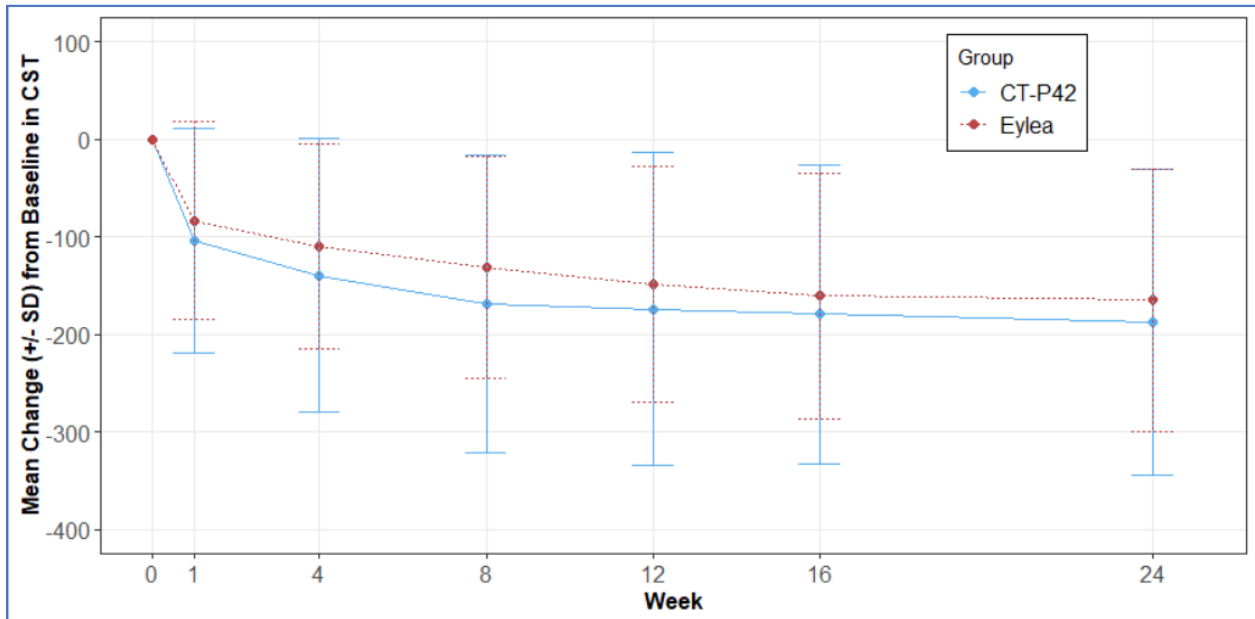


ANCOVA with treatment as factor, and baseline BCVA and country as covariates using FAS.
Source: Reviewer's analysis

Change in CST from baseline as determined by spectral-domain OCT

Figure 6 displays the mean changes of CT-P42 and Eylea in CST. As seen in Figure 6, the CT-P42 group demonstrated a more substantial reduction from baseline in CST compared to the Eylea group during the 24 weeks.

Figure 6: Plot for mean change from baseline in CST over time up to Week 24 (FAS)

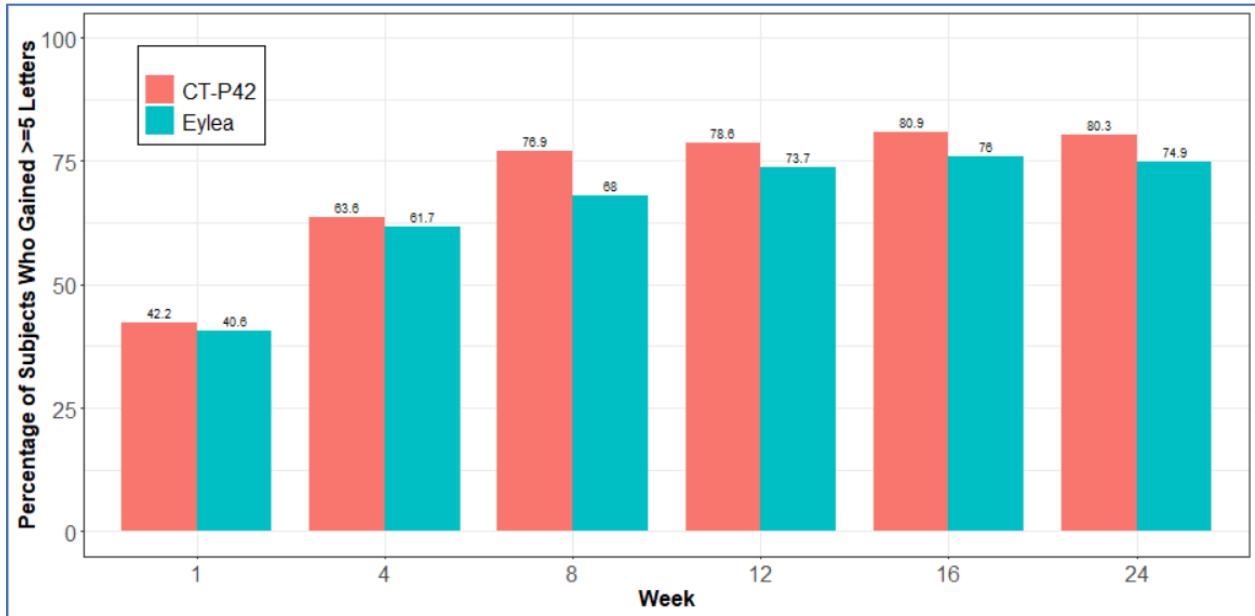


Source: Reviewer's analysis

Subjects who gained ≥ 5 , ≥ 10 , and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS

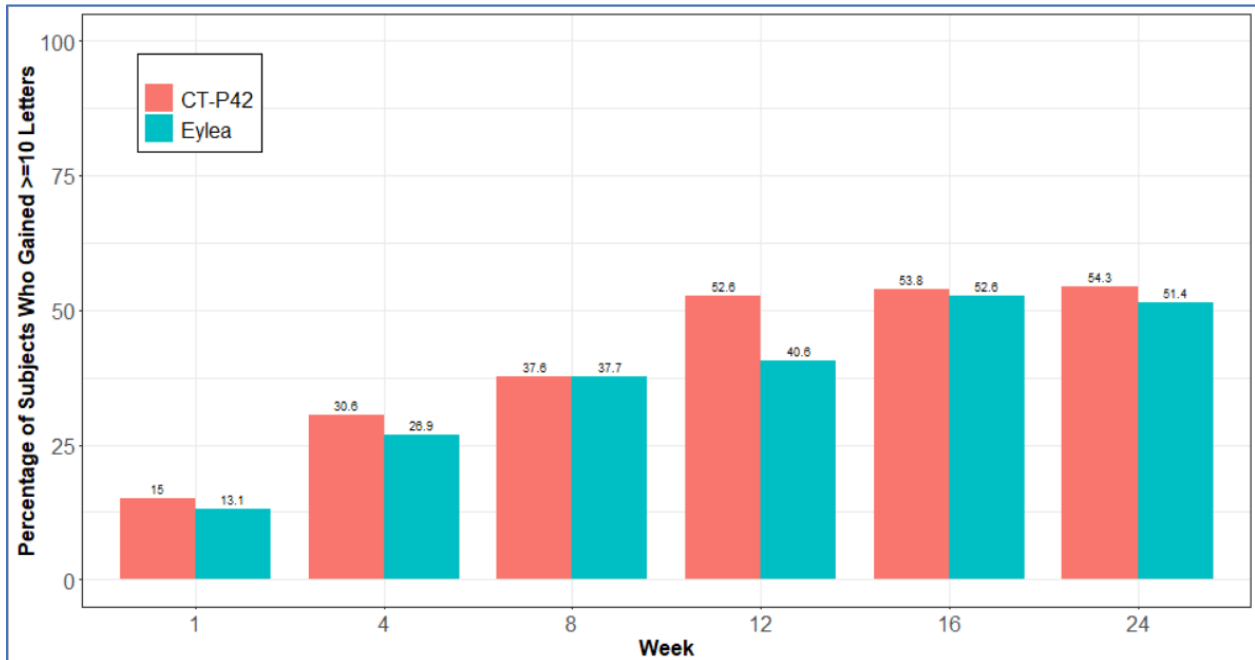
Figures 7,8, and 9 show bar charts which illustrate the proportions of subjects who gained ≥ 5 , ≥ 10 , and ≥ 15 letters, respectively, in BCVA over time up to Week 24. The proportions of subjects who gained ≥ 5 , ≥ 10 , and ≥ 15 letters in BCVA over time up to Week 24 appear to be comparable between two groups. In general, positive trend were observed in the proportions of patients achieving gains of ≥ 5 , ≥ 10 , or ≥ 15 ETDRS letters from baseline up to Week 24.

Figure 7: Bar chart for the proportion of subjects who gained ≥ 5 letters in BCVA over time up to Week 24 (FAS)



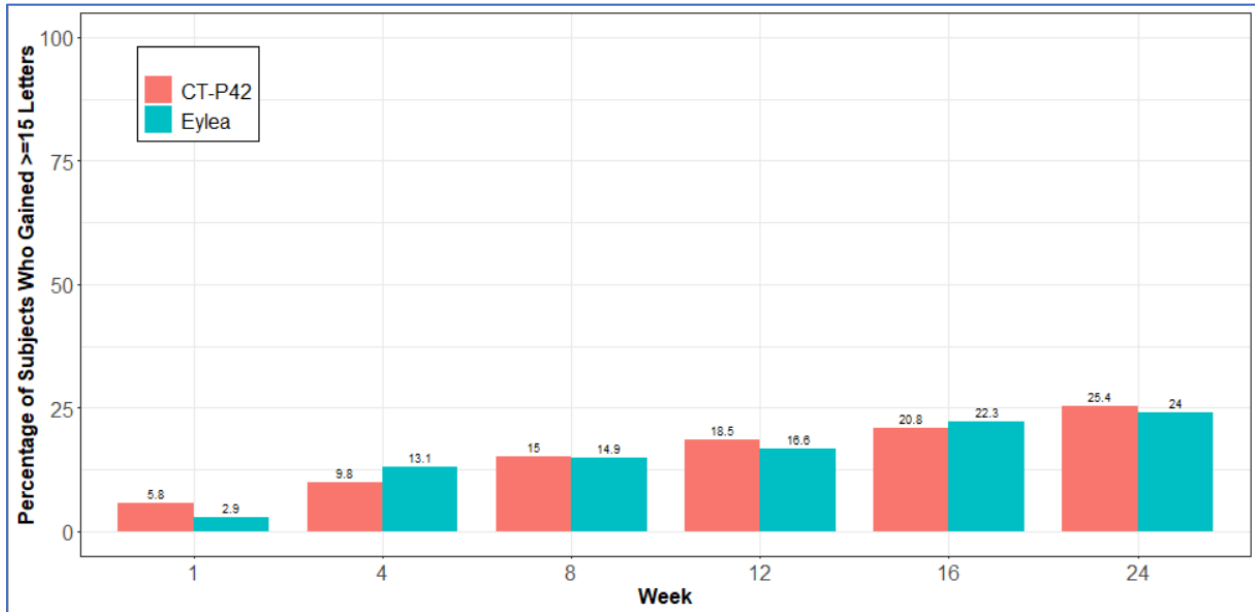
Source: Reviewer's analysis

Figure 8: Bar chart for the proportion of subjects who gained ≥ 10 letters in BCVA over time up to Week 24 (FAS)



Source: Reviewer's analysis

Figure 9: Bar chart for the proportion of subjects who gained ≥ 15 letters in BCVA over time up to Week 24 (FAS)

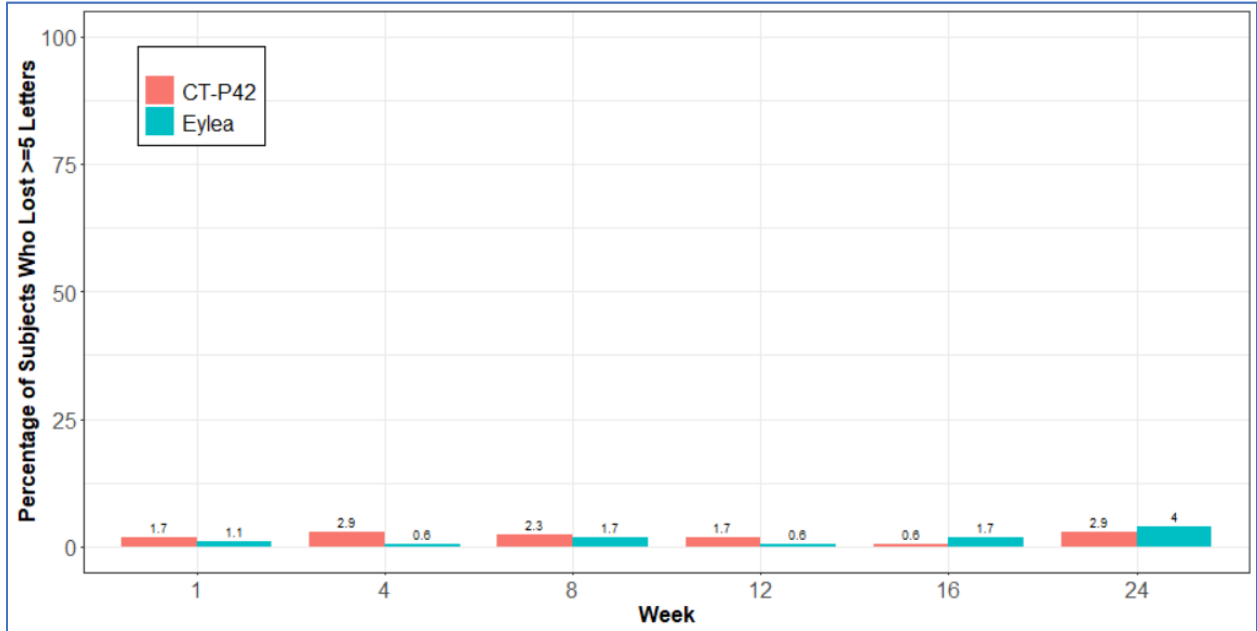


Source: Reviewer's analysis

Subjects who lost ≥ 5 , ≥ 10 , and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS

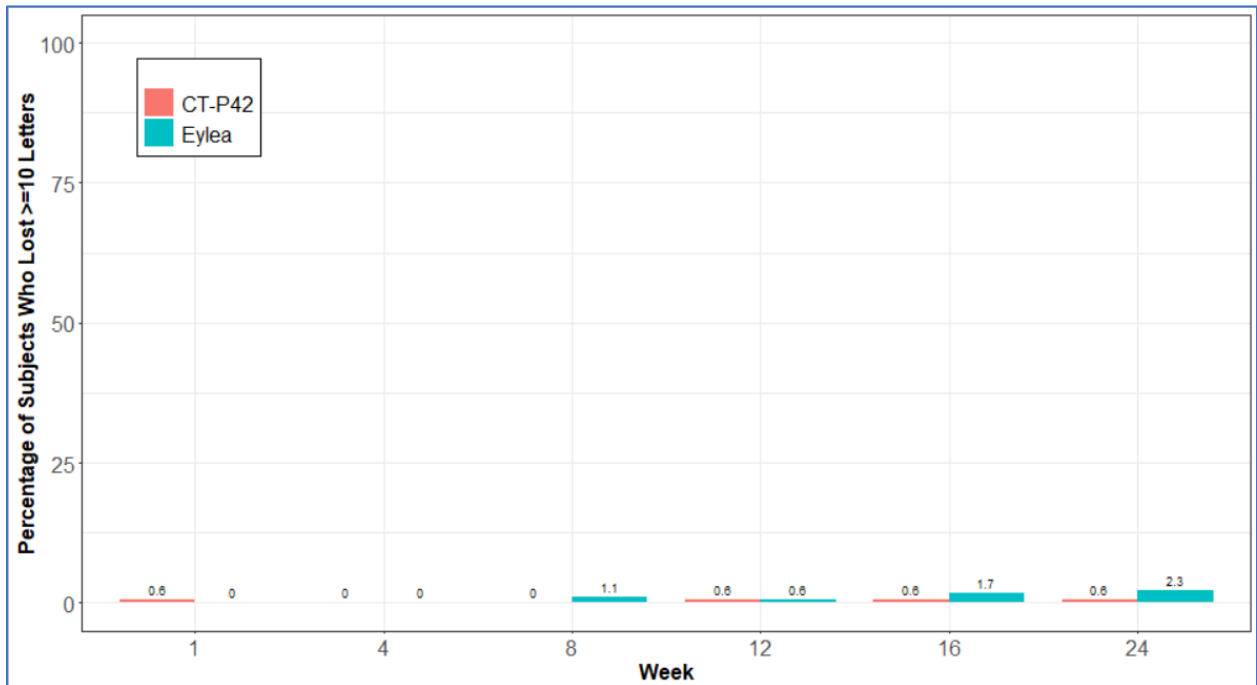
Figures 10, 11, and 12 show bar charts which illustrate the proportions of subjects who lost ≥ 5 , ≥ 10 , and ≥ 15 letters, respectively, in BCVA over time up to Week 24. The proportions of patients who lost of ≥ 5 , ≥ 10 , and ≥ 15 letters from baseline were lower than 5% of the FAS

Figure 10: Bar chart for the proportion of subjects who lost ≥ 5 letters in BCVA over time up to Week 24 (FAS)



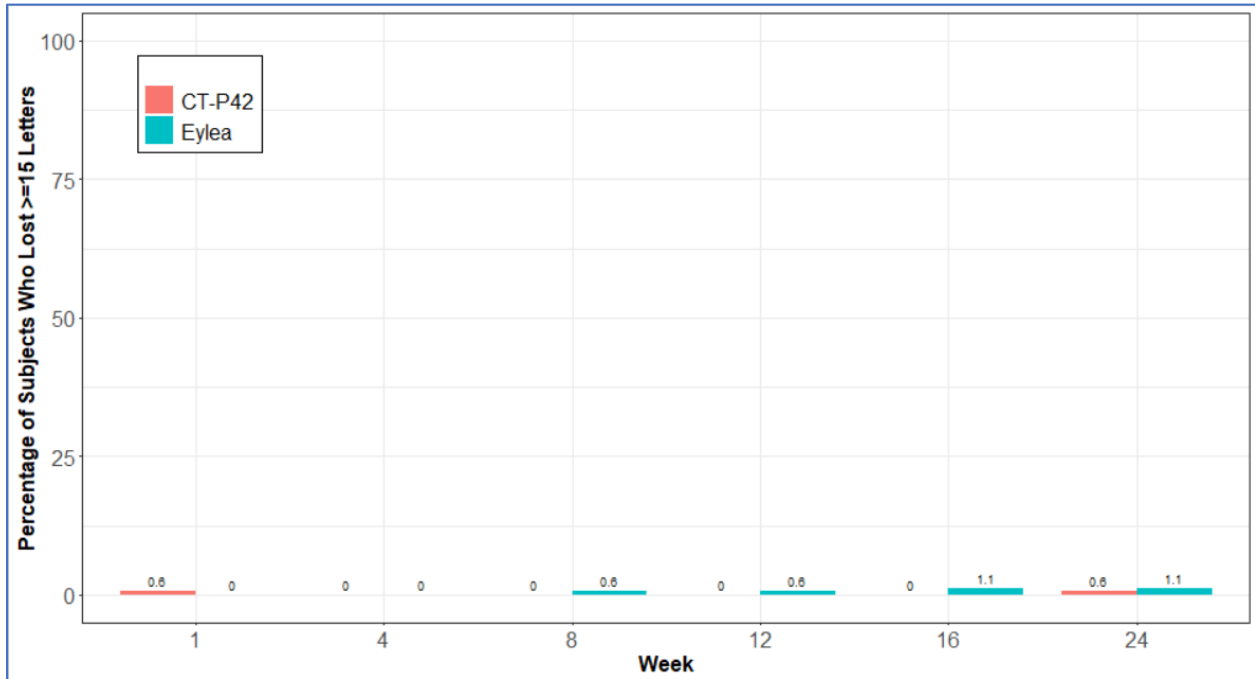
Source: Reviewer's analysis

Figure 11: Bar chart for the proportion of subjects who lost ≥ 10 letters in BCVA over time up to Week 24 (FAS)



Source: Reviewer's analysis

Figure 12: Bar chart for the proportion of subjects who lost ≥ 15 letters in BCVA over time up to Week 24 (FAS)



Source: Reviewer's analysis

Patients with ≥ 2 -step improvement from baseline in the ETDRS DRSS score as assessed by FP

Patients with ≥ 2 -step improvement from baseline in ETDRS DRSS score for the FAS is summarized in Table 8. In the FAS, both treatment groups seem to exhibit a similar rise in the percentage of patients achieving a ≥ 2 -step improvement in ETDRS DRSS score.

Table 8: Summary of Patients with ≥ 2 -Step Improvement from Baseline in ETDRS DRSS Score (FAS)

	CT-P42 (N = 173)	Eylea (N = 175)	Total (N = 348)
Week 8, n (%)	27 (15.6)	28 (16.0)	55 (15.8)
Week 24, n (%)	41(23.7)	35 (20.0)	76 (21.8)

Source: Table 11-12 of CSR

3.2.4.3 Efficacy Conclusion

Study 4231 provides adequate statistical evidence to support that there is no clinically meaningful difference between CT-P42 and Eylea with respect to the mean change in BCVA using the ETDRS chart from baseline to Week 8 according to the prespecified similarity margin, [-3, 3]. Sensitivity analyses also confirm the robustness of the primary analysis and support the similarity of CT-P42 and Eylea.

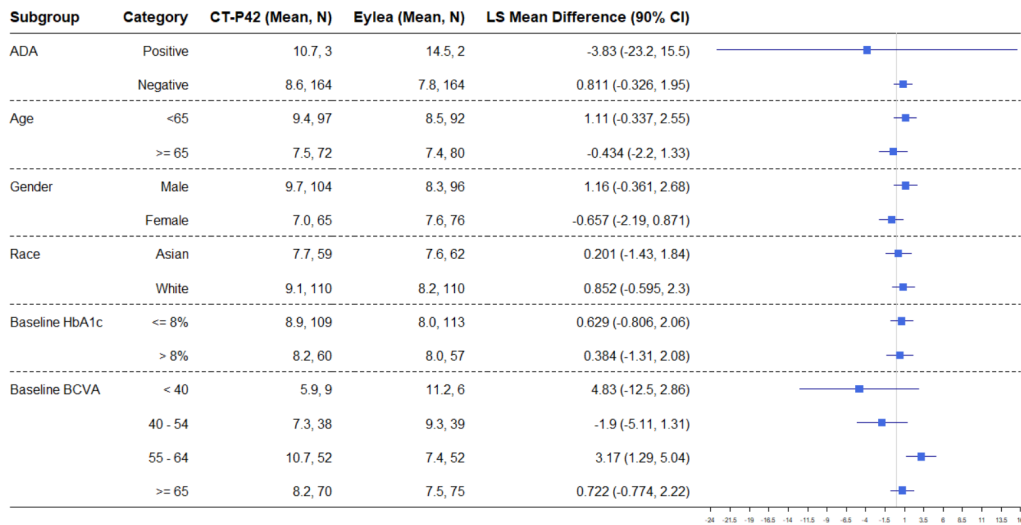
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the primary efficacy endpoint is analyzed across the subgroups defined by the following factors:

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

Figure 13 shows the summary of the adjusted mean changes in BCVA from baseline to Week 8 by the subgroup variables. While some numerical variances noted among the subgroups, these variances were derived from relatively small number of the patients and the results did not indicate any clinically significant trend.

Figure 13: Mean BCVA change from baseline to Week 8 by subgroups (FAS)



LS mean differences and 90% CIs are from ANCOVA model with treatment as a factor, and baseline BCVA, country, and PK subgroup as covariates.

Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer did not identify any major statistical issues that can impact the overall conclusions.

5.2 Collective Evidence

The Applicant is seeking approval for CT-P42 as a proposed biosimilar to US-licensed Eylea (afibercept). Similarity of CT-P42 and Eylea was evaluated in Study 4231.

The primary endpoint was the mean change from baseline to Week 8 in BCVA using the ETDRS chart. The adjusted mean change from baseline to Week 8 was comparable between the two groups (8.90 letters for CT-P42 vs. 8.33 letters for Eylea using FAS; 8.51 letters for CT-P42 and 8.17 letters for Eylea using PP set). The 90% confidence intervals for the mean treatment difference (CT-P42 – Eylea) were (-0.528, 1.660) and (-0.729, 1.420) letters using FAS and PP set, respectively, which were contained within the pre-specified similarity margin [-3, 3]. Thus, the Study 4231 demonstrated the similarity of CT-P42 and Eylea for the primary endpoint.

5.3 Conclusions and Recommendations

Based on the totality of evidence from the Study 4231, the reviewer concludes that the application has provided adequate evidence to support the similarity of the proposed biosimilar

product CT-P42 and Eylea in the primary efficacy endpoint, which is the change from baseline to Week 8 in Best Corrected Visual Acuity (BCVA) measured using the ETDRS chart.

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/

SUNGWOO CHOI
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JEONGSOOK L KIM
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