Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
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	• 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)	Same indications as those approved for US-licensed Eylea: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Proposed Dosing Regimens	Same regimen approved for US-licensed Eylea: **Neovascular (Wet) Age-Related Macular Degeneration (AMD)** • 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. **Macular Edema Following Retinal Vein Occlusion (RVO)**

	• 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). **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)** • 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).
Recommendation on Regulatory Action	APPROVAL of CT-P42, injection, for intravitreal use as biosimilar to US-Eylea (aflibercept) for the products described below: • 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. (b) (4)

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

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 (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 [redacted] 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 [redacted], for PFS DP manufacturing). To address deficiencies identified during pre-license inspection (PLI), Celltrion transferred the manufacture of unassembled PFS DP from [redacted] to Patheon Italia S.p.A. Ferentino, Italy (FEI 3004110157) and the assembly process was transferred from [redacted] 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 ± 3°C.
  PFS: 24 months when stored at 5 ± 3°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

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 Ul. 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.

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. [redacted (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 [redacted (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 [redacted (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 [redacted (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 [redacted (b) (4)] with the US-Eylea PFS under these specific circumstances.[1]

The review team recommends [redacted (b) (4)] that:

[1] See FN 2 *supra*.

- (b) (4)
-

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.

(b) (4)

(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.

(b) (4)

(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