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	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	• 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)	Same indications as those approved for US-licensed Eylea: • Neovascular (Wet) Age-Related Macular Degeneration • Macular Edema Following Retinal Vein Occlusion • Diabetic macular edema • Diabetic retinopathy
Proposed Dosing Regimens	Same regimen approved for US-licensed Eylea: Neovascular (Wet) Age-Related Macular Degeneration (AMD) • The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). • Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week (monthly) dosing after the first 12 weeks (3 months). • Although not as effective as the recommended every 8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. Macular Edema Following Retinal Vein Occlusion (RVO) • The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly).

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

Reviewers of Biosimilar Application

BLA 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
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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 (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.

	Discipline	Primary	Secondary
OPQ Review Team	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

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**.

(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 (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:

- (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 "*injection*" 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 *"allow for proper identification of the product."* For more information see Guidance for industry *"Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.c"*	Add the dosage form "*injection*" 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 (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. (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

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**.

(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
03/26/2025 01:22:00 PM

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

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 Name[1]	Aflibercept-boav
Proposed Proprietary Name[1]	EYDENZELT
Pharmacologic Class	vascular endothelial growth factor (VEGF) inhibitor
Applicant	Celltrion, Inc.
Applicant Proposed Indication(s)	Indicated for the treatment of patients with: • 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

[1]Section 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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Reviewers of Biosimilar Multidisciplinary Evaluation and Review

Regulatory Project Manager	Dheera Semidey
OTBB Scientific Reviewers	Milalynn Victorino, FNP-BC Michelle Luo, M.D, Ph.D.
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
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OSI CSO	Roy Blay
OPDP Reviewer	Carrie Newcomer
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

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 [redacted] 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 [redacted].

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). [redacted]

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 [redacted] 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 [redacted].

Table 1 Summary and Assessment of Biosimilarity [redacted]

Comparative Analytical Studies[2]	
Summary of Evidence	• 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	• There are no residual uncertainties from a product quality perspective.

[2]Refer 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	• 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	• There are no residual uncertainties from a non-clinical perspective.
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• 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	• There are no residual uncertainties from a clinical pharmacology perspective.
<u>Clinical Studies</u>	
Summary of Evidence	• 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	• There are no residual uncertainties from the clinical or clinical statistical perspectives.

[redacted] (b) (4)

(b) (4)	
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical or clinical statistical perspective.
Any Given Patient Evaluation	
Summary of Evidence	• 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	• There are no residual uncertainties from the clinical perspective.
Extrapolation	

Summary of Evidence	• 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 [redacted] • 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 [redacted] biosimilar to US-Eylea for the following indications for which US-Eylea has been previously approved: o Neovascular (Wet) Age-Related Macular

	Degeneration (AMD) o Macular Edema Following Retinal Vein Occlusion (RVO) o Diabetic Macular Edema (DME) o Diabetic Retinopathy (DR) [redacted]
Assessment of Residual Uncertainties	• 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 [redacted]

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 [redacted] 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 [redacted] 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] [redacted]

- 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 prelude 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.

		Strategy for immunogenicity testing was acceptable with recommendation to bank samples for future assessments.
05/18/2022	Advice/Information Request Letter	[redacted]
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 [redacted].
7/12/2023	Advice/Information Request Letter	The Agency provided clarification on information other than [redacted].
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 [redacted].

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	**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	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	**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 ・**Randomized: 348 patients** - CT-P42: 173 - EU-Eylea: 175 **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 CT-P42: **31** patients

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 (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of

endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, which blocks the VEGFR-1 and VEGFR-2 downstream signaling cascade associated with pathological angiogenesis and vascular leakage. Potency of the CT-P42 is assessed using two bioassays: (i) ELISA to measure its VEGF-A165 binding activity and (ii) cell-based assay to measure its VEGF blockade activity. 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 PlGF 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 [redacted]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
[redacted] mM sodium phosphate	-
5% w/v sucrose	-
0.03% w/v polysorbate 20	0.03%w/v polysorbate 20
[redacted] mM sodium chloride	[redacted] mM sodium chloride
-	[redacted] mM histidine (0.038 mg [redacted]Histidine, 0.033 mg L-Histidine monohydrochloride monohydrate
-	10% trehalose
pH 6.2	pH 6.2

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

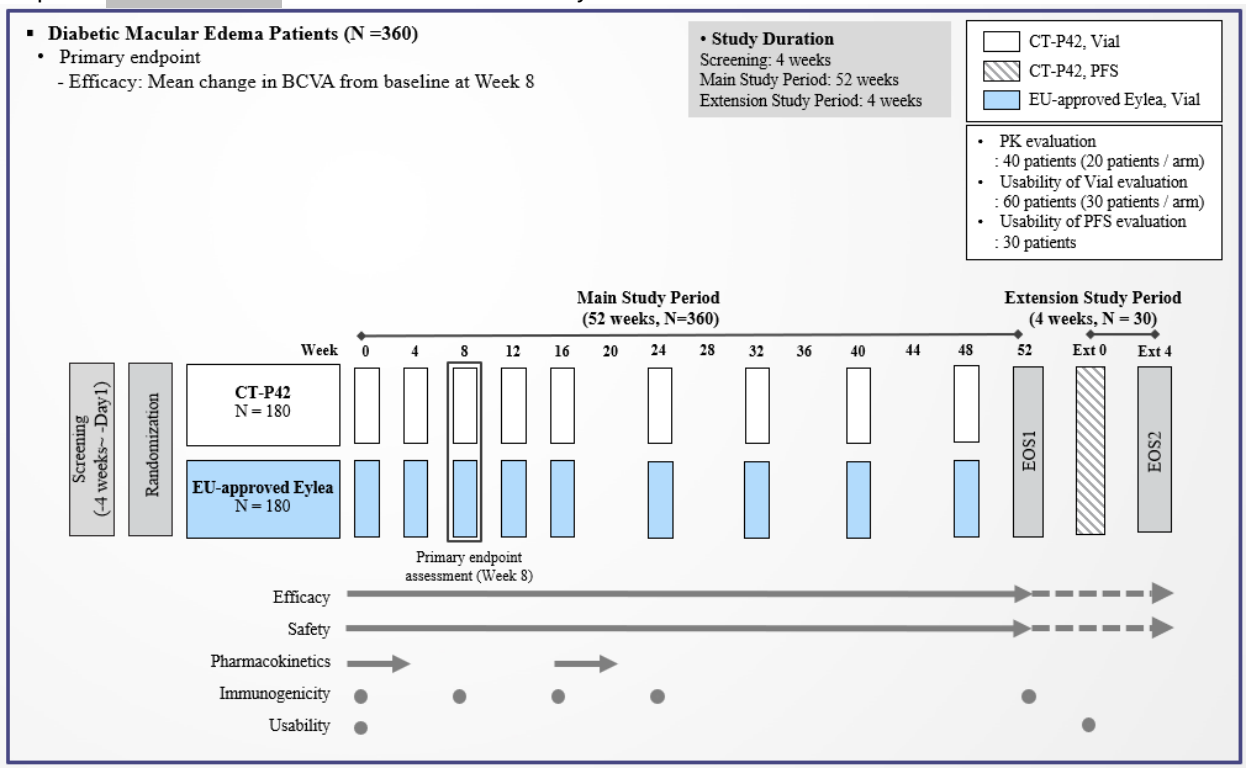
A PK similarity study using traditional PK endpoints, such as AUC and Cmax, in healthy subjects is not considered to be feasible for the following reasons: 1) aflibercept is administered by intravitreal injection directly into the eye to treat diseases that are localized to the eye and the systemic exposures 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



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

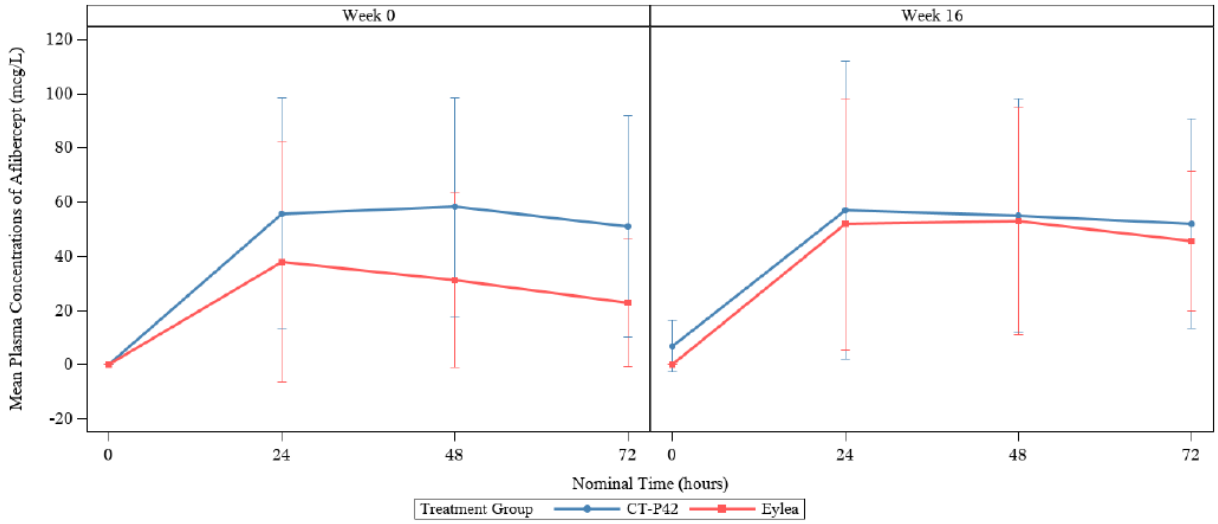
Plasma concentrations of study drugs were measured using a validated meso scale discovery (MSD)-electrochemiluminescence (ECL) immunoassay. The lower and upper quantification limits of the assay were 16 ng/mL and 1024 ng/mL, respectively. All PK samples were analyzed within the established stability 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

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 (α = 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 ≤ 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

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

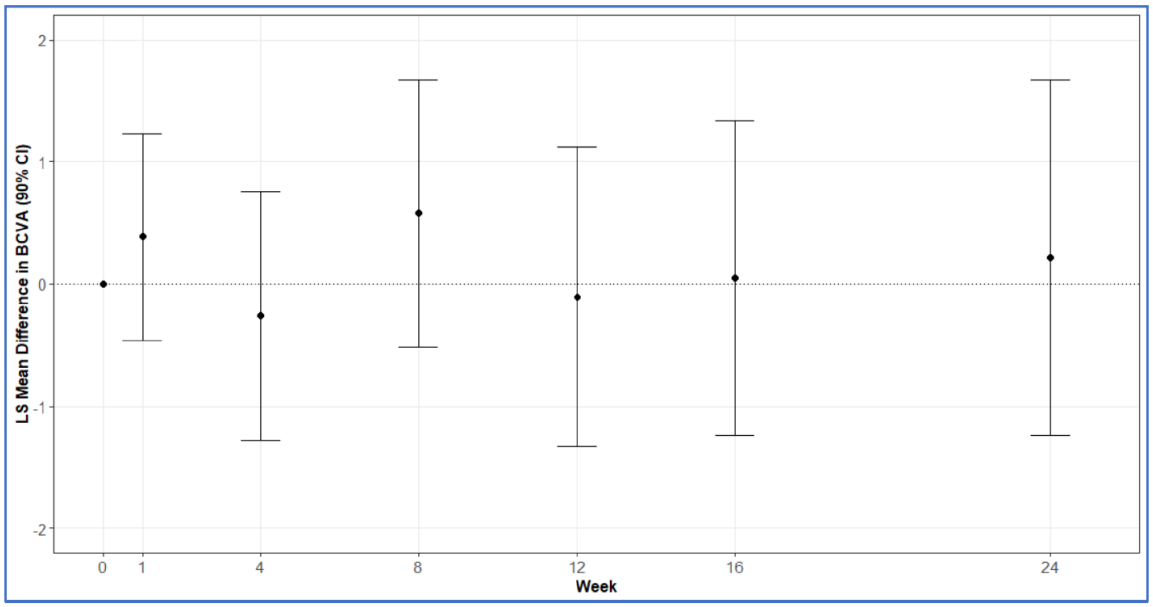
Analysis Population	Method	LS Mean (SE)		Difference (CT-P42 - Eylea)	
		CT-P42 (N = 173)	Eylea (N = 175)	Mean (SE)	90% CI
FAS	MI with the MAR assumptions [1]	9.44 (0.799)	8.84 (0.775)	0.60 (0.663)	**(-0.49, 1.69)**
FAS	MMRM [2]	9.36 (0.725)	8.76 (0.721)	0.60 (0.638)	**(-0.45, 1.65)**
FAS	ANCOVA using 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

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)

(b) (4)

(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

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, [redacted] 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).

[redacted] 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. [redacted]

2. (b) (4)

3.

4.

(b) (4)

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

Facility Inspection

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

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

3. Inspection of the [redacted] is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

Additional Microbiology comments

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 [redacted]. The risk of this event to DP microbial contamination is not fully understood and should be thoroughly evaluated. For example, it is not clear which [redacted], frequency and duration of this potential CCI breach or whether the event has any CCI impact.

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 ☒	No ☐ (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: _____		

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 ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒ No ☐	No ☐ (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
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MICHELLE T LUO
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