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RESEARCH**

APPLICATION NUMBER:

761377Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA 761377 Resubmission Executive Summary
Review Number: 3
Assessment Date: 08/20/2025

1. Application/Product Information

BLA number	761377 (Seq. 0047)
Submission Type	Class II Resubmission: Second Complete Response Resubmission
Regulatory Pathway	351(k) Biologics License Application Proposed biosimilar (b) (4) product to US-licensed Eylea (aflibercept)
Associated IND/BLA	PIND 147335 Refer to meeting minutes dated June 22, 2020, August 30, 2021, August 15, 2022, and August 31, 2023, and August 26, 2024, for BPD Type 1, 2 and 4 meetings between the applicant and the Agency.
Review Designation	Standard Complete Response Resubmission (Second resubmission)
Applicant	CELLTRION, Inc.
Indication	Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: EYDENZELT (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 with a (b) (4)) PFS: 0.5 mL (b) (4) syringes with (b) (4) rubber plunger stoppers and (b) (4) rubber luer lock tip caps with (b) (4).		
Co-packaged Product Information	A vial kit contains one 18 gauge x 1½ inch sterile filter needle (5 µm), one 1 mL sterile Luer lock plastic syringe, and one 30 gauge x ½ inch sterile injection needle.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Barry Gertz	Samuel Mindaye
	Drug product		
	Facility/Microbiology	Ekaterina Allen	Zhong Li (facility) Maxwell Van Tassell (Microbiology)
	RBPM	Kristine Leahy	
	ATL	Samuel Mindaye	
OPQ Issued Consults	None		

Regulatory history: The original BLA 761377 submission for CT-P42 (afibercept, proposed biosimilar to US-licensed Eylea) received a Complete Response (CR) recommendation on June 27, 2024, due to deficiencies that included product quality, microbiology, and facility deficiencies (at Celltrion, Inc., Korea DS manufacturing, and at (b) (4), for PFS DP manufacturing). To address deficiencies identified during pre-license inspection (PLI), Celltrion transferred the manufacture of unassembled PFS DP from (b) (4) to Patheon Italia S.p.A. Ferentino, Italy (FEI 3004110157) and the assembly process was transferred from (b) (4) to Steripack Medical, Poland. Based on these changes, a complete response to the Agency's CR letter was re-submitted on September 26, 2024 (seq. 0038). The information and data provided in seq. 0038 and subsequent amendments were reviewed and the manufacturing sites (DS at Celltrion, Inc., Korea, and PFS DP at Patheon Italia S.p.A. Ferentino, Italy) were inspected. While the PLI of the DS site (Celltrion, Inc., Korea) confirmed compliance, the status of the DP facility at Thermo Fisher Scientific (Patheon Italia S.p.A.), Ferentino, Italy (FEI: 3004110157) concluded with a withhold recommendation. The ATL for the first round CR resubmission is provided in DARRTS (uploaded on March 25, 2025). Therefore, the first CR resubmission received another CRLs on March 26, 2025. Then, Celltrion along with Thermo Fisher Scientific (Patheon Italia S.p.A.) resolved the deficiencies described in the Post-Application Action Letter (PAAL, from March 28th, 2025), and resubmitted BLA 761377 CR for the second time on April 18, 2025 (S/N0047). This executive summary covers the product quality review of the second round CR resubmission.

2. Recommendation and Conclusion on Approvability

Recommendation: Approval

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

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:**
Celltrion Inc. (Plant (b) (4), (FEI 3005241015)
(b) (4) Academy-ro, Yeonsu-gu,
Incheon, 22014, Republic of Korea
- **Drug Product:**
PFS: Patheon Italia S.p.A. (FEI 3004110157)

Via Morolense 5,
Ferentino, 03013, Italy

Vial: Patheon Italia SpA, (FEI# 3003065803)
Viale Gian Battista Stucchi 110,
Monza, 20900, Italy

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

c. Dating Period:

- **Drug Product:**

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

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

- **Drug Substance:** (b) (4) months when stored at (b) (4) $^{\circ}\text{C}$.

- **Vial kit components**

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

- **Stability Option:**

For stability protocols:

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

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

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

4. Basis for Recommendation

a. Summary:

BLA 761377 was originally submitted on June 29, 2023 for CT-P42 (afibercept-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. For FDA's review of the information provided in BLA 761377 (original submission and successive resubmission), refer to the assessment of the product quality including the comparative analytical assessment in the following database.

- **Original BLA:** product quality primary: BLA 761377 Review Memo 04092024.PDF, Microbiology and facility: **DS:** B761377 DS Micro Review-OPMA and **DP:** BLA_761377_Celltrion_Final_DP-OPMA),
- **First cycle resubmission:** product quality BLA STN 761377 Resubmission Review and Microbiology and facility Resub-BLA761377-OPMA-Micro-and-Facility
- **Second cycle resubmission:** microbiology and facility reviews BLA761377-resub-47_Celltrion_DP-1

- **ATL Executive Summary provided in DARRTS:** Original BLA on June 20, 2024 and first cycle resubmission March 25, 2025.

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

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

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

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

Summary of Establishment Information

Facility name and address	FEI	Responsibilities and profile code(s)	Status
CELLTRION Inc. (b) (4) Academy-ro, Yeonsu-gu, Incheon, N/A, Republic of Korea, 22014	3005241015	Production of CT-P42 drug substance, Release testing of CT-P42 drug substance, Stability testing of CT-P42 drug substance, Storage of the (b) (4), Testing of CT-P42 (b) (4), Release testing of CT-P42 drug product, Stability testing of CT-P42 drug product	Approve - Based on Waiver granted by OPMA/OBP
CELLTRION Inc. (b) (4) Academy-ro, 51 beon-gil, Yeonsu gu, Incheon, N/A, Republic of Korea, 22014	3005241015	Release of CT-P42 drug substance, Release testing of CT-P42 drug substance, Stability testing of CT-P42 drug substance, Testing of CT-P42 (b) (4), Storage of the (b) (4) Release testing of CT-P42 drug product, Stability testing of CT-P42 drug product, Release of CT-P42 drug product, Holding and storing of CT-P42 drug product	Approve - Based on Waiver granted by OPMA/OBP
BioReliance Ltd. Todd Campus, West of Scotland Science Park, Glasgow, Lanarkshire, Scotland, G20 0XA	3005343934	Production of the (b) (4), Testing of the (b) (4)	No Evaluation Necessary

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

b. Subdiscipline Recommendation:

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

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

d. Potency Assessment for Labeling:

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

5. Life-Cycle Considerations

- a. Established Conditions based on ICH Q12 principles: No
- b. Drug Substance:



(b) (4)

- ii. Residual risk: None
- iii. Future inspection points to consider: Refer to PLI recommendation.

Drug Product:

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

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

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/

SAMUEL MINDAYE
08/21/2025 03:42:45 PM

BLA 761377 Resubmission Executive Summary
Review Number: 2
Assessment Date: 03/24/2025

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 with a (b) (4)) PFS: 0.5 mL (b) (4) syringes with (b) (4) rubber plunger stoppers and (b) (4) rubber luer lock tip caps with (b) (4) .		
Co-packaged Product Information	A vial kit contains one 18 gauge x 1½ inch sterile filter needle (5 µm), one 1 mL sterile Luer lock plastic syringe, and one 30 gauge x ½ inch sterile injection needle.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Barry Gertz	Samuel Mindaye
	Drug product		
	Facility/Microbiology	Ekaterina Allen	Zhong Li (facility) Maxwell Van Tassell (Microbiology)
	RBPM	Kristine Leahy	
	ATL	Samuel Mindaye	

OPQ Issued Consults	CDRH consult ICCR# 01026470
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Regulatory history: The original BLA 761377 submission for CT-P42 (afibercept, 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](#)).

2. 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.

3. 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 (afibercept-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)
- 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)

(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 OPQAI 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 (afibercept-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.

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/

SAMUEL MINDAYE
03/25/2025 01:02:01 PM

Recommendation: Complete Response

BLA Number: **761377**

Review Cycle: **1**

Review Date: April 15, 2024

Revised to incorporate inspection recommendation: June 17, 2024

Drug Name/Dosage Form	EYDENZELT (aflibercept-boav), injection
Strength/Potency	2 mg/0.05 mL (40 mg/mL) single-use vial and a pre-filled syringe (PFS)
Route of Administration	Intravitreal injection
Rx/OTC dispensed	Rx
Indication	Same indications as reference product (US-licensed aflibercept)
Applicant/Sponsor	CELLTRION, Inc.

Executive Summary Addendum

The Integrated Quality Assessment (IQA) uploaded on April 15, 2024, provided a preliminary recommendation of "approval" pending the outcome of the pre-license inspections (PLI) for the CT-P42 drug substance manufacturer, Celltrion Inc. (Plant ^{(b) (4)} FEI 3005241015), and pre-filled syringe (PFS) drug product manufacturer, ^{(b) (4)}. This IQA Addendum summarizes the outcome of these PLIs, provides the final Facilities recommendation, updates the recommendation of EYDENZELT manufacturing from sterility assurance perspective, and provides a final **complete response recommendation** from the OPQ team. The updated sections are below. Refer to the [DS Celltrion June 17 2024, PFS ^{\(b\) \(4\)} June 14 2024](#), and Quality Executive Summary (uploaded to DARRTS on 04/15/2024) memorandum for all other review sections.

I. Recommendation and Conclusion on Approvability:

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

Microbiology

1.



(b) (4)

2.

3.

4.

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

would be evaluated upon receipt of the complete response. Please work with the DMF holder in resolving the related deficiencies.

Facility Inspection

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

Additional Microbiology comments

We have the following comments/recommendations that are not approvability issues.

Based on the information submitted in your response to Q.20 of our information request on 03/14/2024 (Attachment 3) it appears that (b) (4)

(b) (4). The risk of this event to DP microbial contamination is not fully understood and should be thoroughly evaluated. For example, it is not clear which (b) (4), frequency and duration of this potential CCI breach or whether the event has any CCI impact.

Establishment Information:

Overall Recommendation: Withhold			
Facility name and address	FEI	Responsibilities and profile code(s)	Status
Drug substance			
CELLTRION, Inc. (b) (4) Academy-ro, Yeonsu-gu , Incheon, N/A, Republic of Korea, 22014	3005241015	Drug substance: Production of CT-P42 DS; Release testing of CT-P42 DS; Stability testing of CT-P42 DS; Testing of the MCB and WCB; Storage of the MCB and WCB; Testing of CT-P42 (b) (4) bulk. Drug product Vial: DP storage, release, and stability testing PFS: DP storage, design controls, release, and stability testing	Withhold - Based on Inspection
Bioreliance Ltd. Todd Campus, Glasgow, Lanarkshire, United Kingdom, G20 0XA	3005343934	Production of the (b) (4); Testing of the (b) (4)	No Evaluation Necessary
Bioreliance Ltd. Innovation Park, Hillfoots Road, Stirling, N/A, United Kingdom, FK9 4NF	3005619549	Storage of the (b) (4)	No Evaluation Necessary
BioReliance Ltd Pentlands Science Park, Penicuik, N/A, United Kingdom, EH26 0PZ	3005619544	Testing of the (b) (4)	No Evaluation Necessary
WuXi Advanced Therapies Inc., 400 Rouse Blvd, Philadelphia, PA 19112	(b) (4)	Testing of (b) (4)	Approve - Based on Previous History
Samsung Biologics 300, Songdo bio-daero , Incheon, Yeonsu-gu, Republic of Korea, 21987	3010479596	Testing of (b) (4)	Approve - Based on Previous History
Drug product			
Patheon Italia S.p.A Viale Gian Battista Stucchi 110, Monza, 20900, Italy	3003065803	Vial: DP manufacture, storage, release testing (endotoxin and sterility only), (b) (4) bioburden and endotoxin testing.	Approve - Based on Previous History with Post-Approval Inspection (PoAI) follow up
STERIPACK MEDICAL POLAND SP. Z O. O. Ul. Japonska 1, Leg, 55-220, Poland	3007766601	Vial: secondary packaging (labeling and cartoning), incoming controls of vial kit device components PFS: cartoning and storage of fDP	No Evaluation Necessary
CELLTRION Pharm, Inc. 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea	3012279978	Vial: secondary packaging (labeling and cartoning) PFS: cartoning and storage of fDP	
(b) (4)			Withhold - Based on Inspection
			Approve - Based on Previous History

(b) (4)	
	PLI recommended
	Approve - Based on Previous History
	Approve - Based on Previous History
	Approve - Based on Previous History

Facilities:

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

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

A pre-license inspection and a CGMP inspection of Celltrion Inc., facility (FEI: 3005241015) were conducted from 2/19/2024-2/27/2024. Significant deficiencies were observed in the quality system related to the manufacture of CT-P42 drug substance. At the conclusion of the inspection, form 483 with 10 observations was issued to the firm. The identified issues include: (1) procedures designed to prevent microbiological contamination of products purporting to be sterile did not include adequate validation of the (b) (4) (b) (4) (2) inadequate biosafety testing laboratory operation, (3) lack or not following procedures designed to prevent microbiological contamination of sterile products, (4) responsibilities and procedures pertaining to the Quality Unit are not in writing or fully followed, (5) lack of assurance that DS manufacturing operations in Building (b) (4) are appropriately designed to prevent contamination and cross-contamination of the products manufactured in the facility, (6) written records of investigations into unexplained discrepancies do not always include appropriate conclusions and follow-up, (7) Quality Unit is not fully exercising its authority and/or responsibilities to provide adequate oversight throughout GMP manufacturing operations, (8) lack of appropriate controls over computers or related systems, (9) deficient calibration

verification of laboratory instruments used in routine analysis. At the time of original IQA summary write up, Celltrion Inc., facility (FEI: 3005241015) had a pending Official Actions Indicated (pOAI) alert based on PLI observation and the ORA compliance review was ongoing. On June 12, 2024, ORA completed their compliance review and recommended OAI status. This addendum memo was written to finalize the facility assessment section of the review.

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

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

In addition, an inspection of the (b) (4) facility (FEI# (b) (4)) is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

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

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/

SAMUEL MINDAYE
06/20/2024 12:21:14 AM

BLA Executive Summary

Assessment Date: 04/12/2024

1. Application/Product Information

BLA number	761377
Submission Type	Original submission
Regulatory Pathway	351(k) 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, for BPD Type 2 and 4 meetings held 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
	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 consisting 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 contain 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. CT-P42 is produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology.		
Dosage Form	Injection (solution)		
Strength	2 mg/0.05 mL (40 mg/mL)		
Route of Administration	Intravitreal injection		
Primary Container Closure System	Vial: Glass vial (2 (b) (4) vial, type (b) (4) clear glass), stopper (13 mm, (b) (4) rubber), and cap (13 mm, aluminum seal with a (b) (4)) PFS: 0.5 mL (b) (4) syringes with (b) (4) rubber plunger stoppers and (b) (4) rubber luer lock tip caps with (b) (4) .		
Co-packaged Product Information	A vial kit contains one 18 gauge x 1½ inch sterile filter needle (5 µm), one 1 mL sterile Luer lock plastic syringe, and one 30 gauge x ½ inch sterile injection needle.		
	Discipline	Primary	Secondary
	Drug substance	Hao Kiet Phan	Samuel Mindaye
	Drug product		
	Comparative Analytical Assessment (CAA)		

OPQ Review Team	Immunogenicity Assay	Gunther Boekhoudt	
	Facility/Microbiology	Holly Brevig (Drug Substance) Ekaterina Allen (Drug Product)	Zhong Li (facility) Maxwell Van Tassell (Microbiology)
	RBPM	Kristine Leahy	
	ATL	Samuel Mindaye	
OPQ Issued Consults	CDRH consult ICCR# 00936491		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval pending the outcome of pre-license inspection

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

3. CMC Information for Action Letter

a. Manufacturing Location:

- Drug Substance:**

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

- Drug Product:**

- PFS:** ^{(b)(4)}

- **Vial:** Patheon Italia SpA, (FEI# 3003065803)
Viale Gian Battista Stucchi 110,
Monza, 20900, Italy
- b. Fill size and dosage form:** 2 mg/0.05 mL (40 mg/mL), Injection.
- c. Dating Period:**
 - **Drug Product:** Vial: 36 months when stored at $5 \pm 3^{\circ}\text{C}$.
PFS: 24 months when stored at $5 \pm 3^{\circ}\text{C}$.
 - **Drug Substance:** (b) (4) months when stored at (b) (4) $^{\circ}\text{C}$.
 - **Vial kit components**
 - **Component:** 1½ inch 5 µm sterile filter needle
 - **Component:** 1 mL sterile Luer lock syringe
 - **Component:** ½ inch sterile injection needle
 - **Stability Option:**
 - For stability protocols:
 - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process performance qualification lots.
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- d. Exempt from lot release:**
 - Yes, CT-P42 is exempted from lot release per FR 95-29960.
- e. Draft Phase 4 (Post-Marketing) Commitments (PMCs), Requirements, Agreements, and/or Risk Management Steps, as applicable:** None

4. Basis for Recommendation

a. Summary:

CT-P42 (aflibercept-xxxx) is developed as a proposed (b) (4) to US-licensed Eylea for the same strength, dosage form, indications, and route of administration as for the 2 mg/0.05 mL strength of US-licensed Eylea. CT-P42 is a recombinant fusion protein consisting of domain 2 from human VEGFR-1 and domain 3 from VEGFR-2 fused to the Fc portion of human IgG1. VEGF-A and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PIGF, which blocks the VEGFR-1 and VEGFR-2 downstream signaling cascade associated with pathological angiogenesis and vascular leakage.

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

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

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

Manufacturing of CT-P42 DS is

(b) (4)

The overall CT-P42 process control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for CT-P42 as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for the proposed for drug substance manufacturing (Celltrion Inc., FEI 3005241015), PFS drug product manufacturing ((b) (4)), and vial

drug product manufacturing (Patheon Italia SpA, Monza, Italy; FEI# 3003065803). The proposed DS and DP manufacturing and testing facilities are under review based on the recent relevant inspectional coverage. Pending the outcome of pre-license inspection, the BLA is approvable from product quality, facility, microbiology, and sterility assurance perspectives. Individual assessments for each discipline are located in separate documents in panorama.

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

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

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

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:



(b) (4)



- ii. Residual risk: None
- iii. Future inspection points to consider: Refer to PLI recommendation.

c. Drug Product:

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

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.

APPENDIX. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

Celltrion proposed CT-P42, a 2 mg/0.05 mL (40mg/mL) strength provided in both a single-dose prefilled syringe (PFS) and a single-dose vial presentations, as a (b) (4) biosimilar to the US-licensed Eylea (aflibercept) reference product for intravitreal injection. The single dose vial is co-packaged with or without injection kit components (filter needle, syringe, injection needle). CT-P42 has the same strength, dosage form and route of administration to the US-licensed Eylea. However, the composition of CT-P42 formulation differs from that of US-licensed Eylea in excipients. CT-P42 contains histidine, sodium chloride, trehalose, and polysorbate 20 while US-licensed Eylea contains sodium phosphate, sodium chloride, sucrose, and polysorbate 20.

Celltrion provided results of the three-way CAA studies to support a demonstration that CT-P42 is highly similar to US-licensed Eylea, notwithstanding minor differences in clinically inactive components, as well as to establish the analytical component of scientific bridge between CT-P42, US-licensed-Eylea and EU-approved-Eylea. The CAA was consistent with the FDA Guidance for Industry, Development of Therapeutic Protein Biosimilar: Comparative Analytical Assessment and Other Quality-Related Considerations, May 2019. As part of the assessment, an extensive analytical characterization of CT-P42, EU-approved Eylea, and US-licensed Eylea was performed, which included comparisons of primary structure, post-translational modifications, glycan profiles, purity, product-related variants, higher order structure, protein concentration, and biological function properties of quality attributes (Table 1). Attributes were selected based on the established quality target product profile for US-licensed Eylea and the defined critical quality attributes (CQAs) for CT-P42. Orthogonal methods were implemented and were designed to be capable of detecting analytical differences between the products if present. The methods used in the assessment were confirmed to be suitable for their intended purposes.

The attributes were ranked by criticality and current knowledge of the mechanism of action and assessed accordingly by quantitative and qualitative approaches. From attributes measured by physicochemical assays, protein concentration and primary structure were rated with high criticality score and attributes such as glycosylation, aggregates and fragments, and disulfide bond received moderate criticality ranking. The remaining attributes were rated as very low, and low. From the attributes measured by biological assays, VEGF-A receptor binding (blockade activity of VEGF-A165, binding to VEGF-A165, VEGF-A121, VEGF-A110, and VEGF-A206) received a high/very high criticality score while VEGF-B (VEGF-B167 and VEGF-B186 binding), PIGF binding (PIGF-1 and PIGF-2 binding), and galectin-1 binding received moderate score. The various Fc binding attributes were deemed low criticality because CT-P42 actions do not require Fc effector functions.

For CAA, quality range methods were employed to very high, high, and moderate risk quality attributes. Very high criticality attributes were assessed using the quality range method with multiplier $k = 2$, while high and moderate criticality attributes were assessed using the quality range method with multiplier $k=3$. The multipliers have been scientifically justified. The analytical similarity is considered to have been demonstrated, if 90% or greater of data points for the test product were within the quality range of the US-licensed Eylea or EU-approved

Eylea. Raw data/graphical comparisons were employed to the lowest risk quality attributes or those quality attributes that cannot be quantitatively measured. Such assessment also applies for data from orthogonal tests of attributes that have also been analyzed using the quality range approach (see Table 1 below for more information).

Celltrion included 10 lots (4 vial lots and 6 PFS lots) each of the US-licensed Eylea and EU-approved Eylea in the CAA program. For CT-P42, 10 independent CT-P42 DP lots (4 from vial and 6 lots from PFS presentation) were included in the three-way similarity assessment. The lots were selected from a range of expiration dates and product ages to adequately capture lot-to-lot variability. CT-P42 lots were manufactured between 2021 and 2023. The expiration dates for US-licensed Eylea lots were between June 2021 and February 2024 and EU-approved Eylea lots expire between February 2022 and April 2024. For the DP lots that were close to the 24-month expiration, the materials were aliquoted and frozen at -80°C (stability study of frozen samples was provided). Several CT-P42 and Eylea lots used in the clinical studies were also included in the CAA. When necessary, results are reported relative to a reference standard. A total of two reference standards (one preliminary reference standard and 1 in-house primary reference standard lot) were used, and data were provided to adequately qualify and bridge the reference standards.

In addition, the CAA included comparative stability studies, which evaluated the stability profile (i.e., degradation pathways and rates) of CT-P42 and US-licensed Eylea and EU-approved Eylea under accelerated, stressed, and forced degradation conditions using orthogonal stability-indicating methods. The quality attributes assessed, and storage conditions selected were supported by development studies and risk assessments. The comparative stability studies demonstrate that CT-P42 has similar degradation profile to that of US-licensed Eylea and EU-approved Eylea. In conclusion, Celltrion performed an adequate CAA that evaluated a comprehensive array of quality attributes relevant to CT-P42 and US-licensed Eylea by appropriate methods, used an appropriate data analysis plan, and selected appropriate lots for the assessment. Although some differences are observed in a limited number of quality attributes, the results from this assessment, which are described below, support a demonstration that CT-P42 is highly similar to US-licensed Eylea, notwithstanding minor differences in clinically inactive components.

Additionally, the three-way pairwise comparisons of CT-P42, US-licensed Eylea and EU-approved Eylea were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from clinical studies using EU-approved Eylea as the comparator to the assessment of biosimilarity. Celltrion supported the establishment of the analytical component of the scientific bridge using the same methods and statistical approaches used to support the demonstration that CT-P42 is highly similar to US-licensed Eylea. Based on review of the data, we conclude that the analytical component of the scientific bridge was established.

Refer to Section E – Same Strength(s) below for addition comments regarding the comparison of strength, dosage form, and route of administration between CT-P42 and US-licensed Eylea.

B. Results of Comparative Analytical Assessment

The results from the CAA are summarized in Table 1 below. While not illustrated in the table below, the stability profile of CT-P42 was demonstrated to be similar to that of US-licensed Eylea.

Table 1. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed		Test Method	Supports a Demonstration of Highly Similar	
Primary Structure and post-translational modifications	Molecular weight		LC-ESI-MS	Yes	
	Amino acid sequence			Yes	
	peptide mapping			Yes	
	N-terminal sequence			Yes	
	C-terminal sequence			Yes	
	Oxidation			Yes	
	Deamidation			Yes	
	Isoaspartate content		RP-HPLC	Yes	
	Extinction coefficient		UV spectrophotometry (SoloVPE)	Yes	
Glycation & Glycosylation	Glycation Analysis		HPLC-UV	Yes	
	N-linked glycan identification		Procainamide labeling by LC-ESI-MS	Yes	
	Oligosaccharide Profiling	Fucosylated	HILIC-UPLC	Yes	
		Afucosylated		Yes	
		Galactosylated		Yes	
		High Mannose			
		Sialylated		Yes	
	Sialic Acid (NANA) and N-glycolylneuraminic acid (NGNA) Analysis	NANA	RP-HPLC	Yes	
		NGNA		Yes	
	Glycosylation at Asn36, Asn68, Asn123, Asn196 and Asn282		Reduced CE-SDS	Yes	
Aglycosylation at Asn282 and Asn68		LC-MS	Yes		
Purity and product-related variants	Size heterogeneity	Monomer	SE-HPLC/ SEC-MALS/SV-AUC	Yes	
		HMW species		Yes	
		Charge heterogeneity	Main species	Non-reduced CE-SDS	Yes
			Impurity		Yes
	Charge heterogeneity		Main species	icIEF	Yes
			Acidic species		Yes
		Basic species	Yes		
		pI	Yes		
Higher order structure and biophysical properties	Disulfide bonds		LC-ESI-MS	Yes	
	Free thiol		Measure-IT Thiol assay	Yes	
	Secondary structure		Far UV CD	Yes	
	Tertiary structure		Near UV CD	Yes	
	Secondary structure		FTIR	Yes	
	Thermal stability		DSC	Yes	

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Test Method	Supports a Demonstration of Highly Similar
	Aggregate characterization	SEC-MALS	Yes
	Aggregate characterization	SV-AUC	Yes
Quantity	Protein concentration*	SoloVPE	Yes
Biological properties/ Fc Binding	In vitro Anti-proliferation activity	Cell-based assay (HUVEC)	Yes
	Cell-based hVEGF blockade activity	Cell-based hVEGF blockade	Yes
	VEGF-A165 binding	ELISA	Yes
	VEGF-A121 binding		Yes
	VEGF-A110 binding		Yes
	VEGF-A189 binding		Yes
	VEGF-A206 Binding		Yes
	VEGF-B167 binding		Yes
	VEGF-B186 binding		Yes
	PlGF-1 binding		Yes
	PlGF-2 binding		Yes
	Galectin-1 binding Affinity	SPR	Yes
	VEGF-B 167 binding		Yes
	FcγRIIIa (V-type) Binding Affinity		Yes
	FcγRIIIa (F-type) Binding Affinity		Yes
	FcγRIIIb Binding Affinity		Yes
	FcγRIIa binding		Yes
	FcγRIIb binding		Yes
	FcγRI binding affinity		Yes
	FcRn binding affinity		Yes
	C1q binding	ELISA	Yes
	ADCC activity	Cell-based assay	Yes
	CDC activity		Yes

Comparative assessment of the forced degradation stability studies was performed to evaluate potential differences in the degradation profiles between CT-P42, US-licensed Eylea, and EU-approved Eylea lots when stored under thermal stress ($45 \pm 5^\circ\text{C}$), acidic stress ($\text{pH } 2.5 \pm 0.2$, $2 - 8^\circ\text{C}$), basic stress ($\text{pH } 10.0 \pm 0.2$, $2 - 8^\circ\text{C}$), oxidative stress (Hydrogen peroxide 0.01% , $2-8^\circ\text{C}$), and photo stress ($25 \text{ w/m}^2\cdot\text{hr}$, $25 \pm 2.5^\circ\text{C}$, $60 \pm 5\% \text{ RH}$). Considering the data and justifications for the minor differences observed, the results do not preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea.

C. Analytical Studies to Support the Use of a Non-US Licensed Comparator Product

The clinical development program to support the biosimilarity of CT-P42 to US-licensed Eylea includes one comparative clinical study conducted in patients with DME. Clinical Study CT-P42 3.1 (comparative clinical study) is a double-masked, randomized, active-controlled, parallel-

group study to compare efficacy and safety of CT-P42 and EU-approved Eylea in patients with Diabetic Macular Edema (DME).

Based on the data provided to support analytical similarity of CT-P42 to US-Eylea, CT-P42 to EU-approved Eylea, and EU-approved Eylea to US-licensed Eylea from comparative structural, physicochemical, and biological studies, an adequate analytical component of the scientific bridge between CT-P42, US-licensed Eylea, and EU- approved Eylea was established, which justifies the relevance of the clinical data generated using EU- licensed Eylea as the comparator product. For the CAA studies, the same analytical methods used for the assessment of highly similar between CT-P42 and US- licensed Eylea were used for comparison of CT-P42 and EU-Eylea and EU- approved Eylea and US- licensed Eylea. The differences observed in a subset of quality attributes in the CAA (See section D below) do not preclude a determination that the analytical component of the scientific bridge is established.

D. Assessment of Comparative Analytical Study Results

Of the quality attributes listed in Table 1 above, several quality attributes did not meet the pre-determined similarity acceptance criteria (i.e., at least 90% of CT-P42 lots must be within the quality range) or showed variable results in qualitative assessments (Table 3.2.R.3-1, Section 3.2.R.3 in eCTD Module 3); however, adequate justification has been provided that the differences observed do not preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea. These instances are described below:

Posttranslational modifications

- Deamidation:** Among the eleven deamidated Asn residues, four (Asn68, Asn84, Asn91 and Asn99) are located within the VEGF receptor domain region (VEGFR1 domain 2 and VEGFR 2 domain 3). Raw data comparison revealed deamidation levels at most sites in CT-P42 samples were similar or slightly lower than US- licensed Eylea or EU- approved Eylea. The deamidation of Asn84 in CT-P42 lots was 9.4-11.5% was significantly lower than that of US-licensed Eylea (23.9-25.4%) and EU- approved Eylea (22.4-25.7%). Forced degradation study under high pH stress (pH 10.0 for up to 7 days) shows CT-P42 and US- licensed Eylea experienced increase in deamidation at Asn84 by about 5-7% from the respective baseline without impacting biological activities including FcRn binding affinity, FcγRIIIa binding affinity, cell-based hVEGF blockade activity and VEGF-A165 binding activity. Celltrion noted lack of impact in deamidation at Asn84 on safety or efficacy is attributable to the fact that Asn84 is spatially distant from the ligand binding sites. In the manufacture of CT-P42, the level is controlled by isoaspartate assay at release for DS and DP. Overall, the results show the difference in deamidation do not preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.
- Oxidation:** comparison using raw data shows the site-specific oxidation at Met10 (1.0-1.8%) was slightly lower in CT-P42 compared to US licensed Eylea (2.4 – 2.9%) and EU-approved Eylea (2.3 – 3.7%). For oxidation of Met237, CT-P42 was at 1.2 – 1.7%, US-

licensed Eylea was 2.9-3.5%, and EU- approved Eylea samples ranged from 3.0 – 3.9%. None of the methionine residues in VEGF receptor domain including Met10, Met20, Met163, and Met192 are in the binding site. Met237 is in the Fc domain and might partially participate in FcRn binding, but not in FcγRIIIa binding. To assess the impact of difference in oxidation, the data from forced degradation study was evaluated. Under oxidation stress (0.01% H₂O₂ for 12 hours), the extent of oxidation at Met10, Met163, Met192, Met237 and Met413 increased in CT-P42 and US- licensed Eylea without impact on biological activities including FcRn binding affinity, FcγRIIIa binding affinity, cell-based hVEGF blockade activity and VEGFA165 binding activity. The results show the difference in oxidation is unlikely to have significant clinical impact or preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.

- **C-terminal lysine:** in general, the analysis showed the 3 products predominantly lack the C-terminal lysine. The level of intact C-terminal lysine in CT-P42 lots ranged 1.3 – 2.1% while the US- licensed Eylea lots were between 5.2 – 9.1% and EU-approved Eylea lots were between 3.9 – 11.0%. It is notable that C-terminal lysine variants do not have an impact on safety and efficacy as the residual C-terminal lysine is shown to rapidly cleaved off by carboxypeptidase present in the bloodstream. In further support, Celltrion performed a characterization study, where the levels of variants without C-terminal Lys were higher in acidic peaks than in basic fractions. Nevertheless, basic peaks which contained higher levels of variants with C-terminal Lys exhibited comparable biological activities including VEGF-A165 binding activity (ELISA), cell- based hVEGF blockade activity, VEGF-B167 binding activity (ELISA), FcRn binding affinity and PLGF-2 binding affinity to other peak groups of cIEF. Overall, the observed differences do not preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.

In conclusion, while the PTMs assessment confirmed three-way similarity between US-licensed Eylea, CTP42, and EU-approved Eylea, it also identified some differences in the profile of deamidation, oxidation, and C-terminal lysine status. Generally, extensive characterization including assessment of the impact of changes at levels reported in the CAA have confirmed the PTM differences have minimal impact on potency or clinical effect. Therefore, the observed PTMs patterns do not preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.

Charge Variants

- **Isoelectric point:** The cIEF electropherograms of the US-licensed Eylea, CTP-42, and EU- approved Eylea lots show similar pattern with 14 peaks (Peak 1 – peak 14) in common. The calculated pI values of the 14 peaks of CT-P42 fall within similar ranges of US-licensed Eylea and EU- approved Eylea (within ± 0.03 of the pI of the respective min-max range of US- licensed Eylea). There are three additional minor peaks detected only in some CT-P42 lots. These minor peaks were absent in neuraminidase treated CT-P42 showing that these minor peaks contain sialic acid. However, the overall sialic acid content is similar between CT-P42 and Eylea confirming that the contribution of the new peaks is minor. In addition, the biological activities of samples containing various levels of sialic acids were comparable

confirming the three new minor peaks have insignificant impact to preclude b a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.

- Acidic, main, and basic peaks:** The distribution of charge variants in US-licensed Eylea, CT-P42 and EU-approved Eylea samples were grouped into acidic group (before Peak6), main group (Peak6 – Peak8), basic group (after Peak8) and quantified by total peak area. The CT-P42 lots had main peak area within the QR of US-licensed Eylea and EU- approved Eylea. All the CT-P42 lots (100%) had acidic and basic peaks outside of the quality ranges of the US-licensed Eylea and EU-approved Eylea. Specifically, the percentage of acidic and basic peaks in CT-P42 were (31.1 – 34.4%) and (21.6 – 26.3%), respectively. The quality ranges for US-licensed Eylea were 16.98 -20.52% for acidic group and 30.50 – 42.16% for the basic group. To investigate the impact of charge variant difference, these variants (acidic, main, and basic groups) were fractionated using IEC-HPLC. Peptide mapping of fractions from US-licensed Eylea, CT-P42 and EU- approved Eylea revealed the same kinds of molecular variants in each peak fraction, although the relative contents of the variants might be different. The acidic fraction contains relatively higher levels of variants with deamidation at Asn84 whereas the basic fraction contains a higher ratio of C-terminal lysine. There is also enrichment in the level of sialic acid between acidic and basic fractions. CT-P42 has relatively higher level of sialic acid NANA than US- licensed Eylea and EU- approved Eylea (12.31% compared to 10.45% and 10.32% for US-licensed Eylea and EU- approved Eylea, respectively). Following sialidase treatment with neuraminidase, the acidic peak area of CT-P42 was at similar levels to that of US- licensed Eylea and EU- approved Eylea samples. Taken together, the peak characterization and asialylation studies indicated the higher level of acidic peaks in CT-P42 lots was due to high levels of sialic acid and variants with deamidation at Asn84. In contrast, CT-P42 has lower basic fractions due to the lower level of variants with C-terminal lysine (Lys432) (11.9% in US- licensed Eylea, 5.0% in CT-P42, and 13.4% in EU- approved Eylea). To assess the impact of charge variants, a range of biological activity tests were performed side-by-side for individual fractions of CT-P42, US-licensed Eylea, and EU- approved Eylea. The tests include cell-based hVEGF blockade assay, VEGF-A165 binding, VEGF-B167 binding, PlGF-2 binding and FcRn binding affinity. The results revealed each fraction has comparable activity compared to the corresponding unfractionated sample as well as between the three products confirming charge variant difference does not have significant functional impact.

Taken together, the difference in charge variants (profile and levels of charge variants) in CT-P42 are highly unlikely to adversely impact activities related to therapeutic effect in vivo. The charge variant difference does not preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.

Oligosaccharide profiling by HILIC-UPLC

The percentage areas of 23 peaks were quantified and glycan species were grouped as fucosylated, afucosylated, galactosylated, sialylated, and high mannose (Man5). In general, the same glycan moieties were detected in CT-P42, US-licensed Eylea, and EU- approved Eylea lots. However, there were differences in the levels of individual glycan species, and these affected the relative proportion of the glycan groups. CT-P42 lots had fucosylated group in the range of 28.75-29.41%, which was outside of the US-licensed Eylea QR (25.451 – 27.137) or EU- approved Eylea QR (25.639 – 27.131). Conversely, all CT-P42 lots had significantly lower level of afucosylated group at 2.99-3.44% compared to the US- licensed Eylea QR (6.763 – 9.253%) and EU- approved Eylea (7.3820 – 8.750%). Celltrion performed a study to investigate the cause and impact of differences in individual glycosylation patterns and concluded that these changes are unlikely to have significant clinical impact to preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge as discussed below.

- **Afucosylation:** The impact of afucosylation was assessed by spiking highly afucosylated CT-P42 (produced by adding a fucose analogue to the media during cell culture) into an in-house reference standard. The results showed there was a correlation between the level of afucosylated glycans and FcγRIIIa V-type binding affinity. In contrast, no noticeable differences were observed in VEGF-A165 binding activity, Cell-based hVEGF blockade assay and PlGF-2 binding activity between control samples (3.60% afucosylated glycans) and those with 13.93% afucosylated glycans. Overall, the Fc region of the aflibercept molecule does not mediate any CDC or ADCC in vitro and that the FcγRIIIa binding is not related to any known or putative mechanisms of action of aflibercept. Therefore, the observed differences in levels of fucosylated and afucosylated glycans are highly unlikely to have an adverse effect on efficacy or to preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.
- **Galactosylation:** The level of galactosylated glycans in CT-P42 (0.604 – 0.638 mol/mol) was marginally lower than US-licensed Eylea (0.751 – 0.769 mol/mol) and EU- approved Eylea (0.748 – 0.766 mol/mol) but is not expected to adversely impact on potency based on the agalactosylation study which showed comparable biological activities at various levels of galactosylated glycans.
- **High mannose:** The level of high mannose glycans (Man5) in all the CT-P42 lots was within the range 4.74 – 6.39% and is outside of the US-licensed Eylea QR (2.720 – 3.410%) and EU- approved Eylea QR (2.809 – 3.939%). To investigate the impact of high mannose on the biological functions, the three product groups were treated by mannosidase to create samples with different grades of high mannose. Comparative assessment of non-treated vs treated samples evaluated the influence of high mannose on the biological activities. The results suggest the levels of high mannose tested in this study had no significant impact on ligand binding by the VEGF receptor domain or on Fc binding based on binding affinity to FcγRIIIa-V binding affinity and FcRn binding affinity, VEGF-A165 binding activity, VEGF-B167 binding activity and PlGF-2 binding activity as well as cell-based hVEGF blockade activity. Furthermore, US-licensed Eylea, CT-P42 and EU-

approved Eylea had similar biological activities at each of the levels of high mannose tested.

- Sialylation:** When it comes to sialylated glycans, CT-P42 had levels in the range 50.98 – 52.61%, which was marginally outside of the US-licensed Eylea QR (51.520 – 55.892%) and EU- approved Eylea (52.291 – 54.457%). It's notable that aflibercept is a highly sialylated glycoprotein. Nonetheless, nearly half of the 10 batches of CT-P42 were outside the QR of Eylea. To assess the impact of asialylation on biological functions, test samples containing different levels of sialic acids (about 40% - 55%) were prepared by spiking neuraminidase treated samples into untreated control. The study suggest that sialic acid content does not significantly impact FcRn binding affinity, VEGF-A165 binding, VEGF-B167 binding, PlGF-2 binding as well as cell-based hVEGF blockade activity. However, binding to FcγRIIIa-V was modestly increased (by about 30%) as sialic acid content reduced in all 3 products. This increased in FcγRIIIa-V affinity was presumed to be due to the increased G2 level after removal of terminal NANA from G2+NANA and G2+2NANA by sialidase treatment. Furthermore, US-licensed Eylea, CT-P42 and EU- approved Eylea had comparable biological activities at the different levels of sialic acids tested.

Overall, the asialylation and amannosylation study showed that the levels of sialylated and high mannose group glycans did not significantly impact binding to the VEGF receptor domain, cell-based hVEGF blockade activity or Fc receptor binding. The noted differences are not expected to have a clinically meaningful impact because the biological activities of these products are similar. On average the difference in high mannose between the proposed biosimilar and the reference is 2.2% and this percentage is even smaller for sialylation. These changes are unlikely to have significant clinical impact to preclude a demonstration that CT-P42 is highly similar to US-licensed Eylea or the establishment of the analytical component of the scientific bridge.

- Glycosylation at 5 sites (Asn36, Asn68, Asn123, Asn196 and Asn282):** The electropherograms of the reduced CE-SDS showed CT-P42 lots had the same or slightly lower proportion of fully occupied (5 sites) with glycosylation at 52.78 – 58.40% compared with 56.40 – 58.20% in US-licensed Eylea and 55.78 – 57.95% in EU- approved Eylea. Aglycosylation study using LC/MS revealed Asn68 is the predominant site in the 3 products that may not be fully glycosylated and that other sites (Asn36, Asn123, Asn196 and Asn282) were generally nearly 100% glycosylated. Therefore, the variability in glycosylation could be attributed to the varying levels of glycosylation at Asn68. The aglycosylation level at Asn68 in CT-P42 (34.64– 40.78%, with mean 36.69%) is higher than US-licensed Eylea (30.16 –33.52%, mean 31.50%) or EU-approved Eylea (29.65 – 32.52%, mean 31.28%). The biological activities of samples containing various levels of aglycosylated product (43 -56%) shows aglycosylation of US- licensed Eylea, CT-P42 and EU- approved Eylea had a modest reduction (about 20%) in binding affinity of FcγRIIIa-V but had no impact on FcRn binding affinity, VEGF-A165 binding activity, VEGF-B167 binding activity, PlGF-2 binding activity or cell-based VEGF blockade activity. Although the levels of

aglycosylation in aflibercept impacted FcγRIIIa-V binding affinity, the marginal difference in glycosylation (<3%) is highly unlikely to have an adverse impact on the therapeutic activities of aflibercept as the ADCC is not MoA of aflibercept.

Taken together, the extent and profile of glycan modification in US- licensed Eylea, CT-P42 and EU- approved Eylea have been extensively investigated using various orthogonal analytical techniques. The studies revealed the glycation level in CT-P42 was about the same or slightly lower than in US- licensed Eylea and EU- approved Eylea. Deeper characterization of specific site occupancy by various types of oligosaccharides including assessment of the impact of changes at levels reported in the CAA revealed the differences in the level of fucosylated, afucosylated, galactosylated, sialylated and high mannose groups do not mount any significance in the biological activities of these products and not anticipated to have a clinical impact to preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.

Purity & Impurity: Size variants were assessed by SEC-HPLC. The monomer in CT-P42 were in the range of 97.94 – 98.72 and the quality ranges were 97.003 – 98.577 (US- licensed Eylea) and 96.611 – 98.609 (EU- approved Eylea). The high molecular weight variants in CT-P42 were in the range of 1.28 – 2.06, while the quality ranges were 1.423 – 2.997 for US- licensed Eylea and 1.391 – 3.389 for EU- approved Eylea. The low molecular weight species were not detectable in three test groups. Overall, two out of 10 CT-P42 lots were outside of the US- licensed Eylea or EU- approved Eylea margins (slightly lower HMW and slightly higher monomer). The minor difference in the purity (HMW and monomer) between the proposed biosimilar and reference products appear to be favorable for the proposed biosimilar but unlikely to have any clinical impact. The results do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.

Biological activity: The biological activities of US- licensed Eylea, CT-P42 and EU- approved Eylea in binding to VEGF-A165, VEGF-A121, VEGF-A110, VEGF-189, VEGF-A206, VEGF-B167, VEGFB186, PlGF-1, PlGF-2, and Galectin-1 as well as cell-based hVEGF blockade activity and antiproliferation using human umbilical vein endothelial cells (HUVECs) were assessed. While not related to the MoA of aflibercept, binding to C1q, FcRn and FcγR binding affinities were also evaluated. Furthermore, a one-time evaluation of ADCC and CDC of aflibercept was performed. The relative potency and binding activities were determined relative to the in-house CT-P42 primary reference standard. Overall, the biological activity data confirmed similarity between US- licensed Eylea, CT-P42 and EU- approved Eylea and noted the following differences in Fc receptor binding affinity.

- The mean values of relative FcγRIIIa (V-type) binding affinity of US- licensed Eylea, CT-P42 and EU- approved Eylea were 220%, 97% and 222%, respectively (Table 3.2.R.3-46).

- The mean values of relative FcγRIIIa (F-type) binding affinity of US- licensed Eylea, CT-P42 and EU- approved Eylea were 173%, 100% and 180%, respectively (Table 3.2.R.3-47).
- The mean values of relative FcγRIIIb binding affinity of US-licensed Eylea, CTP42 and EU- approved Eylea were 186%, 106% and 190%, respectively (Table 3.2.R.3-48).

Fcγ receptor binding affinity was classified as low risk in terms of criticality, as the MoA of aflibercept does not involve Fc functions. A lower affinity of CT-P42 to some Fcγ subtype receptors is likely due to the notably lower level of afucosylated glycans compared to US-licensed Eylea and EU- approved Eylea. However, because the Fc region of the aflibercept molecule does not mediate any CDC or ADCC in vitro (confirmed using CT-P42 lots), the differences in Fcγ binding affinity are highly unlikely to have any adverse effect on biological activities in vivo. Therefore, the differences in the affinity of CT-P42 to some Fcγ subtype receptors do not preclude a demonstration of highly similar or establishment of the analytical component of the scientific bridge.

E. Same Strength

CT-P42 has the same dosage form and route of administration as US-licensed Eylea. Celltrion is seeking licensure of 2 mg/0.05 mL CT-P42 in PFS presentation and a single dose vial kit with co-packaged injection components (filter needle, syringe, injection needle). US-licensed Eylea is available in this strength (2 mg/0.05 mL) in a single dose vial co-packaged with injection components (filter needle, syringe, injection needle)¹. Comparative protein concentration (mg/mL) was assessed as part of the CAA. The deliverable volume (0.05 mL) and fill weight data were assessed [REDACTED] (b) (4). Based on the comparative protein concentration data and manufacturing data, the proposed presentation has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in unit of mass per unit volume as that of US-licensed Eylea. The strength of 2 mg/0.05 mL CT-P42 in PFS and a single dose vial is the same as that of US-licensed Eylea.

¹ U.S. Prescribing Information, U.S.-licensed Eylea. Accessed November 9, 2023 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s075lbl.pdf

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