CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761165Orig1s000

PRODUCT QUALITY REVIEW(S)

Proposed Interchangeable Biosimilar to US-licensed Lucentis

Recommendation: Approval

EXECUTIVE SUMMARY

BLA 761165-ORIG-1-RESUB-9
Review Number: First round
Review Date: June 2, 2022

Drug Name/Dosage Form	Cimerli (ranibizumab (b) (4)) injection, for intravitreal use
Strength/Potency	• 10 mg/mL: The recommended dose is 0.5 mg (0.05 mL of 10 mg/mL dosage strength) • 6 mg/mL: The recommended dose is 0.3 mg (0.05 mL of 6 mg/mL dosage strength)
Route of Administration	Intravitreal injection
Rx/OTC dispensed	Rx
Indication	All indications currently approved for US-licensed Lucentis
Applicant/Sponsor	Coherus BioSciences Inc. (Originally submitted by Bioeq GmbH. Transferred to Bioeq AG in September 2021, and to Coherus BioSciences Inc. in April 2022)
US Agent	(b) (4)

Product Overview

Cimerli (ranibizumab (b) (4), FYB201) is a recombinant humanized IgG1 isotype antigen-binding fragment (Fab) developed as a biosimilar to US-licensed Lucentis (ranibizumab). Ranibizumab is not glycosylated and does not exhibit antibody-mediated effector functions. Ranibizumab binds to the receptor binding site of all human alternatively spliced Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells resulting in the reduction of endothelial cell proliferation, vascular leakage, and new blood vessel formation. Cimerli (ranibizumab (b) (4)) drug product is manufactured to have the same strength, dosage form, formulation, presentations, and route of administration as US-licensed Lucentis in single-dose vials. Cimerli is a sterile, preservative-free, (b) (4) colorless to pale yellow solution for intravitreal injection supplied in single-dose glass vials containing ranibizumab (b) (4) at 10 mg/mL and 6 mg/mL.

Quality Review Team

Discipline	Reviewer	Office/Division
Drug Substance (DS)	Leopold Kong / Leslie A. Rivera Rosado	CDER/OPQ/OBP/DBRR IV
Analytical Comparability		
Drug Product (DP) and Analytical Method Validation	Andrea Franco	CDER/OPQ/OBP/DBRR IV
Immunogenicity assays	Tao Wang	CDER/OPQ/OBP/DBRR IV
OBP Labeling	Jennifer Kim	CDER/OPQ/OBP
Micro/Facility DS	Yun Wu	CDER/OPQ/OPMA/DBM/BMB1
Micro/Facility DP	Wayne Seifart	CDER/OPQ/OPMA/DBM/BMB1
Team Leads	LCDR Leslie A. Rivera Rosado (Product Quality) Zhong Li (OPMA Facilities) Max Van Tassell (OPMA Micro)	CDER/OPQ/OBP/DBRR IV CDER/OPQ/OPMA/DBM/BMB1 CDER/OPQ/OPMA/DBM/BMB1
Application Team Lead	LCDR Leslie A. Rivera Rosado	CDER/OPQ/OBP/DBRR IV
Regulatory Business Project	Anita Brown	CDER/OPQ/OPRO
OBP Biosimilar Policy	Joel Welch Marlene Schultz-DePalo	CDER/OPQ/OBP-IO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Michael Puglisi	ORO/DROSM
Signatory Authority	Wiley Chamber	OSM/DO
Cross-disciplinary Team Lead	William Boyd	OSM/DO
Clinical Reviewer	Martin Nevitt	OSM/DO
Nonclinical	Maria Rivera	ORDPURM/DPTRDPURM
Clinical Pharmacology	Lei He	OCP/DIIP
Biostatistics	Nam Hee Choi	OB/DBIV
DMEPA SE	Damon Birkemeier	OSE/DMEPA
DMEPA TL	Valerie Vaughan	OSE/DMEPA
DPV SE	Rachna Kapoor	OSE/DMEPA
OSE PM	Oyinlola Fashina	OSE/DMEPA
OSE PM TL	Ameet Joshi	OSE/DMEPA

1. **Names:**
   a. Proprietary name: Cimerli
   b. Trade name: Cimerli
   c. Non-proprietary name: ranibizumab (b) (4)
   d. CAS registry number: 347396-82-1
   e. INN/USAN Name: ranibizumab
   f. OBP systematic name: MABFRAG HUMANIZED (IGG1) ANTI P15692 (VEGFA_HUMAN) [FYB201]

2. **Pharmacologic category:** a vascular endothelial growth factor (VEGF) inhibitor

Submissions Reviewed:

Communication	Date
STN 761165/9- BLA Original Application	08/02/2021
STN 761165/12- Response to IR dated 8/23/2021 (OPMA)	09/02/2021
STN 761165/15- Response to IR dated 11/30/2021 (OPMA)	12/14/2021
STN 761165/16- Response to IR dated 01/19/2022 (OBP)	01/25/2022
STN 761165/17- Response to IR dated 03/04/2022 (OPMA)	03/18/2022
STN 761165/18- Response to IR dated 03/15/2022 (OBP)	03/23/2022
STN 761165/21- Response to IR dated 03/30/2022 (OBP)	04/14/2022
STN 761165/22- Response to IR dated 04/13/2022 (OPMA)	04/20/2022
STN 761165/23- Response to IR dated 04/11/2022 (OBP)	04/21/2022
STN 761165/24- Response to IR dated 05/06/2022 (OBP)	05/20/2022

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF#	DMF Holder	Item Referenced	Code[1]	Status[2]	Date review completed	Comments (status)
(b) (4)			3	N/A	N/A	Not reviewed. Sufficient information related to compatibility with the product provided in the BLA.
			3	N/A	N/A	
			2	Adequate	3/28/2019	
			3	N/A	N/A	Not reviewed. Sufficient information in the BLA.

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")
2. Adequate, Adequate with Information Request, Deficient, or N/A (there are enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: None

3. Consults: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761165-ORIG-1-RESUB-9 for Cimerli (ranibizumab (b) (4)) manufactured by Coherus BioSciences Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Cimerli (ranibizumab (b) (4)) is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Cimerli (ranibizumab (b) (4)) is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location
  - Drug Substance: (b) (4)
  - Drug Product: (b) (4)
- Fill size and dosage form: 0.2 mL/vial (10 mg/mL or 6 mg/mL), injection
- Dating Period:
  - Drug Product: 36 months at 5 ± 3°C, protected from light
  - Drug Substance: (b) (4) months at (b) (4) °C
- 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 first three production lots.
  - We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your drug substance under 21 CFR 601.12.
- Exempt from lot release: Yes, Cimerli is a specified product exempt from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Cimerli (ranibizumab (b) (4), FYB201) is a proposed biosimilar to US-licensed Lucentis for all the same indications as US-licensed Lucentis (i.e., Neovascular (Wet) Age-Related macular Degeneration, Macular Edema following Retinal Vein Occlusion, Diabetic Macular Edema, Diabetic Retinopathy, and Myopic Choroidal Neovascularization). A comparative analytical assessment of FYB201 and US-licensed Lucentis was provided to support the demonstration that Cimerli is highly similar to US-licensed Lucentis. As part of the comparative analytical assessment, the molecular

attributes of ranibizumab were collectively assigned to appropriate assessment categories and a sufficient number of lots of each product were evaluated. A comprehensive array of analytical methods was used to support a demonstration that the products are highly similar. Each method was demonstrated to be suitable to detect and/or quantitate potential differences in critical quality attributes between FYB201 and US-licensed Lucentis. The comparative analytical assessment data provided support the conclusion that Cimerli is highly similar to US-licensed Lucentis.

The overall Cimerli control strategy incorporates control 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 Cimerli are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. Drug substance and drug product facilities operate in compliance with cGMP and are acceptable for manufacturing. The BLA is recommended for approval from a product quality, facility, microbiology, and sterility assurance perspectives.

The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Quality Labeling	-	Pending
Facilities	-	Adequate
Microbiology	-	Adequate
CAA	-	Adequate

D. Environmental Assessment or Claim of Categorical Exclusion:

A claim of categorical exclusion from environmental assessment (EA) according to 21 CFR 25.31(c) was provided and is acceptable.

E. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps:

- Complete DS transport validation study and submit the final transportation validation report. Due: Q3 2023

- Complete DP bulk vial and DP final product shipment validation studies and submit the final transportation validation report. Due: Q3 2023

II. Evaluation of the Comparative Analytical Assessment (CAA)

A. Overview and Conclusions

Coherus is seeking licensure for FYB201 as a biosimilar to US-licensed Lucentis (US-Lucentis). US-Lucentis is licensed in 0.3 mg (6 mg/mL) and 0.5 mg (10 mg/mL) strengths, in single-use vials and single-use pre-filled syringe presentations. Coherus is seeking licensure for both strengths in single-use vial presentations only.

Coherus performed a comparative analytical assessment (CAA) using 19 lots of US-Lucentis (13 lots of 10 mg/mL and 6 lots of 6 mg/mL), and 15 lots of FYB201 (10 lots of 10 mg/mL and 5 lots of 6 mg/mL). Note that not all batches were analyzed for all attributes. The FYB201 lots evaluated included seven 10 mg/mL drug product (DP) batches manufactured at (b) (4) three 10 mg/mL and three 6 mg/mL PPQ batches manufactured at (b) (4) and three 6 mg/mL commercial batches manufactured at (b) (4) Four FYB201 DP batches were not independent regarding DS; these batches were used for protein content determination only. The FYB201 clinical lots included in the CAA were used during the comparative clinical study FYB201-C2015-01-P3 (batches F15144, F15191, F16128, F16290, and F17190, all manufactured at (b) (4)). US-Lucentis lots used in the comparative clinical study were also included in the CAA.
The CAA included the following analyses to support a demonstration that FYB201 is highly similar to US-licensed Lucentis:

- Extensive comparative physicochemical and functional assessments of quality attributes.
- Comparative assessments of the degradation profiles under forced degradation conditions.
- Comparative assessment of the degradation profiles under accelerated and stressed temperature conditions.

Data generated from the studies using EU-approved Lucentis were not used to support a demonstration of biosimilarity. Therefore, the analytical testing results from lots of EU-approved Lucentis submitted in the BLA were not assessed, as there was no need to establish a scientific bridge.

Coherus used a risk-based approach for the statistical evaluation of the analytical results:

- Very-high, high, and moderate risk-ranked quality attributes for which data output is quantitative were tested using quality ranges (QR).
    - For most attributes, the QR were established based on the results derived from the US-Lucentis lots included for each test method. The upper and lower bound limits of the QR were estimated using a standard deviation multiplier (SDM) of 3. The SDM used to establish each QR was scientifically justified. It is expected that 90% of all batches fall within the respective ranges.
    - For a few quality attributes (i.e., molecular mass [retention time], disulfide linkage [molecular mass], thermodynamic stability [temperature]) pre-defined limits were defined.
- Very-high, high, and moderate risk-ranked quality attributes for which data output is qualitative, were evaluated using side-by-side visual comparison.
- Low risk and very-low ranked quality attributes were tested using quantitative or qualitative assays and were evaluated using side-by-side visual comparison.

Coherus pooled comparative analytical data from the two strengths of 6 mg/mL and 10 mg/mL (of US-Lucentis for the calculation of quality ranges and of FYB201 for the comparative analytical assessment). Pooling of data from US-Lucentis is justified because no relevant differences were observed between US-Lucentis 6 mg/mL and 10 mg/mL. The applicant defined relevant differences as more than one 6 mg/mL US-Lucentis batch not being within the mean ±3SD ranges of the 10 mg/mL US-Lucentis batches. Pooling of data from two strengths of FYB201 is justified as both strengths have the same formulation (b) (4) (b) (4) Pooling of data from 10 mg/mL strength batches manufactured at (b) (4) and 6 mg/mL strength batches produced at (b) (4) is justified as comparability for the two different strengths produced at the different manufacturing sites was demonstrated.

Most analytical methods in the CAA were performed at (b) (4) with several exceptions: (1) SV-AUC analyses were performed at (b) (4) (b) (4) (2) CE-SDS non-reduced analyses was performed at (b) (4) (b) (4) for some batches, other batches analyzed by (b) (4) (3) CE-SDS reduced and CZE were performed at (b) (4) Results from method validation, qualification, or verification studies were provided and adequately support the suitability of each method for its intended use during the CAA.

Coherus also provided data derived from a comparative forced-degradation stability study and a comparative stability under accelerated and stressed temperature conditions.

- Forced degradation conditions included:
  - Temperature stress (60°C/60% relative humidity (RH) for 1 and 2 weeks)
  - Mechanical Stress (4 and 8 weeks 600 rpm at 6°C ± 4°C)
  - Light Stress (≥ 1.2 MLx*h daylight & ≥ 200 W*h/m2 UV and ≥ 3.6 Mlx*h daylight & ≥ 600 W*h/m2 UV; both performed at +25°C ± 3°C, 60% ± 5% RH)
  - Oxidation Stress (4 h and 24 h with 10 mM AAPH at 40°C ± 2°C, 75% ± 5% RH)
  - pH stress-acidic (pH 3 for 1 and 2 weeks at 40°C ± 2°C, 75% ± 5% RH)
  - pH stress-basic (pH 9 for 1 and 2 weeks at 40°C ± 2°C, 75% ± 5% RH)

- Accelerated and stressed temperature conditions included:
  - Accelerated: 25°C/60% RH up to 6 months, inverted
  - Stressed: 40°C/75% RH up to 3 months, inverted

Studies included the evaluation of one each of 6 mg/mL US-Lucentis (31 months old), 10mg/mL US-Lucentis (18 months old), 10 mg/mL FYB201 from (b) (4) (36 months old), 10mg/mL FYB201 from (b) (4) (4 months old), and 6mg/mL FYB201 from (b) (4) (4 months old).

The comparative forced degradation studies support that FYB201 and US-Lucentis have a similar degradation profile.

Based on our assessment of the FYB201 and US-Lucentis data, the results support a demonstration that **FYB201 is highly similar to US-licensed Lucentis**, notwithstanding minor differences in clinically inactive components. Coherus used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of FYB201 and

US-Lucentis to support a demonstration that FYB201 is highly similar to US-Lucentis. The number and type of lots tested and data analysis methods were appropriate to allow for a meaningful evaluation of the results of the CAA. While differences were observed in a limited number of attributes, these do not preclude a demonstration that FYB201 and US-licensed Lucentis are highly similar.

Based on the comparative analytical assessment and manufacturing data, the proposed presentation of FYB201 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as both US-Lucentis vial presentations [0.5 mg/0.05 mL (10 mg/mL) and 0.3 mg.0.05 mL (6 mg/mL)]. Each strength of FYB201 is the same as that of US-licensed Lucentis.

B. Comparative Analytical Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	**Quality Attribute Assessed** (Risk Rank) (- analytical methods)	**Supports a Demonstration of Highly Similar?**
Primary Structure	Amino acid sequence (Very High) – LC-MS/MS and Edman degradation	Yes
	Molecular Mass (High) - LC-MS intact mass	Yes
	Norleucine (Low) – LC-MS peptide map reduced. *This is a well-known modification of methionine residues for proteins from bacteria. Examined HC Met34 and Met84.*	*Yes*
Post-translational modifications	Oxidation (High) – LC-MS peptide map reduced.	Yes
	Pyroglutamate (Low) – LC-MS peptide map reduced (HC Glu1)	Yes
	Glycation (Moderate) –LC-MS intact mass reduced	Yes
	Acetylation (Low) – LC-MS peptide map reduced	Yes
	Methylation (Low) – LC-MS peptide map reduced	Yes
Higher Order Structure	Secondary Structure (High) – Far-UV CD and FTIR	Yes
	Tertiary Structure (High) – Near-UV CD	Yes
	Disulfide mapping (High) – RP-HPLC peptide mapping non-reduced	Yes
	Thermodynamic Stability (Low) – Far-UV CD	Yes
Biological Function (Note Ranibizumab binds to all human VEGF-A isoforms, including proteolytically cleaved VEGF-A_{110}. The most common isoforms are VEGF-A_{165} and VEGF-A_{121})	Inhibition of VEGF-A_{165} induced cell growth (Very High) – HUVEC proliferation assay, Western blot confirmation of inhibition of signaling pathway, inhibition of tissue factor expression in HUVEC, HUVEC migration assay	Yes
	Inhibition of VEGF-A_{121} induced cell growth (High) – HUVEC proliferation assay	Yes
	Inhibition of VEGF-A_{111} induced cell growth (High) – HUVEC proliferation assay	Yes
	Binding to VEGF-A_{165} (Very High) – BLI	Yes
	Binding to VEGF-A_{121} (High) – BLI	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed (Risk Rank) (- analytical methods)	Supports a Demonstration of Highly Similar?
	Binding to VEGF-A_{111} (High) – BLI. Instead of proteolytically cleaved VEGF-A_{110}, commercially available VEGF-A_{111} was used. The difference between the two are in C-terminal region (residues 105-110/111), which are not involved in the binding reaction. *This is acceptable.*	Yes
	Binding to VEGF-A_{189} (High) – BLI	Yes
	Non-binding to VEGF-B, -C, -D and to PlGF (Low) – BLI/ELISA	Yes
Product-related Substances and Impurities	HMW species (High) – SE-HPLC (leading method) and SV-AUC (orthogonal method)	Yes
	LMW species (High) – CE-SDS non-reduced (leading method), CE-SDS reduced and SDS-PAGE non-reduced (orthogonal methods)	Yes
	LC-LC homodimer (High) – SDS-PAGE non-reduced	Yes
	Acidic species (Moderate) – CEX-HPLC (leading method), Capillary zone electrophoresis (CZE) and Isolectric Focusing (IEF) (orthogonal methods).	Yes
	Basic Species (High) – CEX-HPLC (leading method), CZE and IEF (orthogonal methods)	Yes
Drug Product Attributes	Total protein concentration (High) – UV280	*Yes*

Comparative forced degradation stability studies were performed to evaluate potential differences in the degradation profiles between FYB201 and US-Lucentis when stored under temperature stress, mechanical stress, basic pH stress, acidic pH stress, oxidative stress, and light (photo-) stress conditions as defined above. Results support that the degradation pathway and rates of degradation between FYB201 and US-Lucentis are similar when stored under each condition.

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

Not applicable.

D. Assessment of Comparative Analytical Study Results

Comparative analytical assessment acceptance criteria were met for all attributes with the following exceptions:

Critical Quality Attributes with Differences	*Justification for why difference does not preclude a demonstration of highly similar*
Non-canonical amino acid (norleucine)	All FYB201 batches have higher levels of norleucine [(b) (4)]% versus [(b) (4)] for US-Lucentis batches) at heavy chain (HC) methionine 34 (Met_{34}) and [(b) (4)]% versus [(b) (4)]% for US-Lucentis batches at HC Met_{83}. Coherus provided a detailed risk assessment for norleucine:

Critical Quality Attributes with Differences	*Justification for why difference does not preclude a demonstration of highly similar*
	• The norleucine incorporation site Met_{83} is outside of the complementarity-determining region (CDR) loops. Although Met_{34} is within a CDR loop, it is not located in the binding site. Therefore, the risk of impact on activity should be relatively low. • Development batches with higher levels of norleucine show comparable levels of potency to GMP batches. • Analytical data indicate comparable binding and potency of FYB201 and US-Lucentis. • FYB201 samples with enriched levels of norleucine (b) (4) % norleucine at position Met_{34} and (b) (4) % norleucine at position Met_{83}) displayed comparable levels of bioactivity (b) (4) compared to FYB201 drug product (b) (4) • The applicant stated that norleucine incorporation at Met positions is a well-known protein modification for recombinant proteins produced in *E. coli* with prominent examples of approved human therapeutic proteins such as NutropinAQ (rh-GH) and Zarxio (filgrastim, rh-GCSF). It has not been reported that norleucine affects PK, immunogenicity, or safety. In conclusion, the presence of this variant is of relatively low risk in terms of activity. Impact on stability and other quality attributes appear to be minimal, based on the overall quality profile of FYB201. Impact on immunogenicity is unknown; however, considering the low dose and administration route of the drug, the overall risk for immunogenicity should be low. *In general, the results demonstrate higher level of norleucine in FYB201 compared to US-Lucentis; however, given that this modification does not impact activity, does not change on stability, and is well controlled (as acidic peaks by CEX-HPLC), elevated levels of norleucine do not preclude a demonstration that FYB201 is highly similar to US-licensed Lucentis.*
Protein concentration	Comparative analytical results for protein concentration measured by UV/Visible spectrophotometry show that: • One 10 mg/mL batch (n=10) measured at 9.7 mg/mL which is outside the mean ±3 stdev quality range established by US-licensed Lucentis batches (9.8-10.66 mg/mL). • Three 6 mg/mL (n=5) batches measured at 6.4, 6.4, and 6.5 mg/mL, which is outside the mean ±3 stdev quality range established by US-Lucentis batches (5.89-6.32 mg/mL). ○ (b) (4)

Critical Quality Attributes with Differences	*Justification for why difference does not preclude a demonstration of highly similar*
	In the 3/23/22 IR response the applicant provided data (Table 7 of the response) from three additional FYB201 DP batches (one 6 mg/mL [210105] and two 10 mg/mL [210145, 210159]) manufactured at [redacted] (b) (4) after the corrective actions were implemented. • Batch 210105 (6.1 mg/mL) was within the US-Lucentis quality range. • Batch 210145 (9.8 mg/mL) was within the US-Lucentis quality range, but batch 210159 (9.7 mg/mL) was just outside of the US-Lucentis quality range. [redacted] (b) (4) Coherus noted that the protein concentration result for all FYB201 DP batches (10 mg/mL and 6 mg/mL) are well within commonly applied specification limits for content [redacted] (b) (4) • The concentration of all 10 mg/mL FYB201 DP batches reside well within the specification ranges for FYB201 ([redacted] (b) (4) mg/mL) and within [redacted] (b) (4) limits of [redacted] (b) (4) mg/mL) of the target concentration. *Overall, the magnitude by which the two FYB201 DP batches exceeded the 9.8-10.66 mg/mL protein concentration quality range is minor and does not preclude a demonstration that FYB201 is highly similar to US-licensed Lucentis.* *Thus we conclude that FYB201 6 mg/mL and 10 mg/mL have similar protein concentrations as US-licensed Lucentis 6 mg/mL and 10 mg/mL, respectively.*

E. Residual Uncertainties Assessment

Not applicable

F. Same Strength(s)

FYB201 has the same dosage form and route of administration as US-licensed Lucentis. Coherus is seeking approval of 10 mg/mL (0.5 mg/0.05 mL) and 6 mg/mL (0.3 mg/0.05 mL) in single-use vials. US-licensed Lucentis is approved in both strengths [10 mg/mL (0.5 mg/0.05 mL) and 6 mg/mL (0.3 mg/0.05 mL)] in single-use vials and pre-filled syringes[1].

Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. FYB201 DP manufacturing process development data were assessed to confirm the suitability of the vial fill weight control strategy to consistently fill vials with sufficient volume to ensure the withdraw and delivery of the 0.5 mg (0.05 mL) and 0.3 mg (0.05 mL) label claims. Based on the comparative analytical assessment and manufacturing data, the proposed presentation of FYB201 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as both US-licensed Lucentis vial presentations [0.5 mg/0.05 mL (10 mg/mL) and 0.3 mg.0.05 mL (6 mg/mL)].

The strength of FYB201 is the same as that of US-licensed Lucentis.

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[1] U.S. Prescribing Information, U.S.-Licensed Lucentis. Accessed March 10, 2022 from https://www.accessdata.fda.gov/scripts/cder/daf/

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Category	CQA	Risk	Origin	Control Strategy	Other notes
Primary structure	Amino acid sequence and molecular mass	Efficacy, PK/PD, Immunogenicity, Safety	Intrinsic to the molecule	(b) (4)	The manufacturing process/production cell bank is designed to result in the correct amino acid sequence ensuring an active protein.
Higher order structure	Secondary Structure				
	Tertiary Structure				
	Disulfide linkage				
Biological function	Potency: Neutralization of VEGF-A165	Efficacy, Safety			
	Potency: Neutralization of VEGF-A121				These VEGF-isoforms are not prominently involved in the MoA. Ranibizumab binding site and binding behavior are identical to VEGF-A165 but its role in pathological neovascularization and abundance in target ocular tissues is lower.
	Potency: Neutralization of VEGF-A110				
	Potency: Neutralization of VEGF-A189				
Product related	HMW species	Increase the likelihood for	Product related		

substances and impurities		enhanced immunogenicity but also efficacy or PK may be affected.	impurity (b) (4)	(b) (4)	
	LMW species	Fragments may lead to decreased potency. Fragmentation can also influence PK.			
	LC-LC homodimer	Could impact biological activity and PK as well as trigger immunogenic response.			(b) (4)
	Acidic species	Shown to impact product biological activity (potency). Changes in pI could also impact PK.	Product related impurity (b) (4)		
	Basic species				
	Deamidation	Potential impact to potency, PK, and immunogenicity.			
	Oxidation				
	Glycation	advanced glycation end products may elicit immunogenic response	Product related impurity (b) (4)		Glycation was extensively evaluated during protein characterization studies using LC-MS reduced mass.

B. Drug Substance [ranibizumab (b) (4)] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

Category	CQA	Risk	Origin	Control Strategy	Other notes
Formulation	(b) (4)	Product stability (safety, efficacy)	Component of the (b) (4)	(b) (4)	
Process related impurities	HCP	Safety	Derived from (b) (4)		
	DNA	Safety			
	(b) (4)	(b) (4)	Process related impurity (b) (4)		(b) (4)
	Endotoxins	Safety, purity	Potential ingress by microbial contaminations (environment or raw materials)		
	Bioburden				
	Antifoam	(b) (4)	Process related impurity (b) (4)		(b) (4)

- **Description (ranibizumab (b) (4)):**

  Ranibizumab (b) (4) (FYB201) is a recombinant humanized IgG1 kappa monoclonal antibody fragment manufactured in *E. coli*. FYB201 is composed of one light chain (214 amino acid residues) linked by a C-terminal disulfide bond to one heavy chain (231 amino acid residues). The total molecular weight of FYB201 is 48.37 kilodaltons (kDa). The complementarity-determining regions (CDR) of FYB201 are identical to US-licensed Lucentis and facilitates binding to the receptor binding site of all human alternatively spliced VEGF-A isoforms. FYB201 harbors no glycosylation site.

- **Mechanism of Action (MoA):**

  VEGF-A is a key driver of vasculogenesis and angiogenesis upon binding to its receptors, Flt-1 (VEGFR-1) and kinase insert domain receptor (KDR) (VEGFR-2), on the surface of endothelial cells. Binding of VEGF-A to its receptors leads to endothelial cell proliferation, neovascularization, and vascular leakage. The biological activity of VEGF-A is associated with Neovascular (Wet) Age-Related macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), and Myopic Choroidal Neovascularization (mCNV). The clinical efficacy of FYB201 for these indications is mediated by binding to VEGF-A which neutralizes interaction with VEGFR-1 and VEGFR-2.

- **Potency Assay:**

  iLite Assay

  Potency of FYB201 DS is assessed using the iLite assay which measures the biological activity of FYB201 in a luminescence assay based on stable transfected HEK293 cells, carrying pB-UAS-Luc, pBGAL4- Elk1a, pBVEGF- R2 and pTK-NL1.3 constructs (F164 cells). VEGF-A induces the expression of firefly luciferase in the F164 cells by binding to the VEGF R2 expressed in the F164 cells. When FYB201 binds to VEGF-A, VEGF-A is unable to activate the VEGF receptor and the VEGF-A-induced luciferase expression of the cells is inhibited. Luciferase induction is measured directly by the BrightGlo Luminescence Assay, a method that measures induced firefly luminescence. The measured luminescence from firefly luciferase is therefore dependent on the induction of firefly expression by VEGF-A. The relative potency is determined by comparison of the inhibitory effect of the FYB201 test sample to the FYB201 reference standard. The final result is expressed as relative potency of a sample in percent compared to the reference standard. The iLite assay is the only potency assay to be used for release and stability testing of FYB201 commercial batches.

  HUVEC Proliferation Assay

  During development, a HUVEC proliferation assay was used to measure the potency of ranibizumab (both FYB201 and US-Lucentis samples). VEGF-A increases the proliferation of HUVECs by binding to the VEGF-R2. When ranibizumab is bound to VEGF-A165, VEGF-A165 is unable to activate the VEGF receptor and the VEGF-A165 induced proliferation of the cells is inhibited. Cell proliferation is measured indirectly by the CellTiter-Blue cell viability assay, a fluorimetric method that uses the indicator dye resazurin to measure the metabolic capacity of viable cells. Viable cells retain the ability to reduce resazurin to resorufin, which is highly fluorescent. The measured fluorescence is therefore dependent on the number of viable cells per well and is a

measure for proliferation. The relative potency is determined by comparison of the inhibitory effect of ranibizumab to the reference standard, calculated with validated PLA software. The final result is expressed as relative potency of a sample (in Unit/mg) compared to the references standard.

- **Reference Materials:**
  The reference standard (RS) is primarily used as the reference in identity and functional (potency) assays. It is also used to demonstrate system suitability for various QC analytical methods (b) (4)

RS Lot	DS Source	Use	Potency at Qualification (HUVEC)
(b) (4)			

(b) (4)

(b) (4)

- **Critical starting materials or intermediates:**

(b) (4)

- **Manufacturing process summary:**

(b) (4)

(b) (4)

- **Container closure:**

(b) (4)

- **Dating period and storage conditions**:
  The dating period for FBY201 DS is (b) (4) months when stored at (b) (4) °C.

C. Drug Product [Cimerli] Quality Summary:

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

The following table provides a summary of the identification, risk, and lifecycle knowledge management for the drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Category	CQA	Risk	Origin	Control Strategy	Other
General DP properties	Total protein content	Total protein content in drug product is essential for clinical efficacy, PK/PD, immunogenicity and safety of the product.	Content of the active ingredient in the (b) (4)	(b) (4)	
	pH	Safety	pH is a result of DS/DP composition		
	Osmolality	Safety	Osmolality is a result of DS/DP composition		
	Clarity	Safety	Clarity indicates absence of particles that may result from degradation or contamination		
	Color	Safety	Color indicates correct DS/DP composition and absence of degradation		
	Sterility	Safety, Purity	Manufacturing process, Container closure integrity (b) (4)		For long term stability, sterility testing according to USP <71> is conducted at time 0 and at 36 months.

	Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	
	Container closure integrity	Safety (sterility assurance)	Container closure integrity (b) (4)		CCI testing according to HVLD is conducted according to USP <1207> at time 0 and 12 month intervals to 36 months.
	Visible particles	Safety	Potential contribution from excipients, primary packaging and process material		
	Subvisible particles	Safety, immunogenicity	Potential contribution from environment, excipients, primary packaging and process material		
	Excipient content	Product stability	Excipient content reflects DP composition		(b) (4)
Specific DP properties	Leachables	Safety	Process related impurity potentially leaching from materials		
	Fill volume	Efficacy, safety	Fill accuracy		

- **Potency and Strength:**
  Cimerli is supplied in a (b) (4) glass vial containing (b) (4) mL (nominal fill volume) of either 6 mg/mL (0.3 mg dose vial) or 10 mg/mL (0.5 mg dose vial) ranibizumab for intravitreal (IVT) injection. Potency is defined as the percent neutralization of VEGF-A (preventing its binding to VEGFR) relative to the current WRS. The potency assays are the same as described for DS.

- **Summary of Product Design:**
  Cimerli (ranibizumab (b) (4)) is a sterile, colorless to pale yellow solution in a single-dose glass vial. Cimerli is supplied as a preservative-free, sterile solution in a single-dose container designed to deliver 0.05 mL of 10 mg/mL ranibizumab (b) (4) (0.5 mg dose vial) or 6 mg/mL ranibizumab (b) (4) (0.3 mg dose vial) aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5. Cimerli is intended for intravitreal injection using a 5-micron sterile filter needle (19-gauge x 1-1/2 inch), a 1-mL Luer lock syringe and a 30-gauge x ½ inch sterile injection needle. Each single-dose vial contains 0.05 mL deliverable volume (0.5 mg dose) of 10 mg/mL or 6 mg/mL ranibizumab- (b) (4) 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20 at pH 5.5.

- **List of Excipients:**
  Histidine HCl, α,α-trehalose dihydrate and polysorbate 20 are all compendial excipients.

- **Reference Materials:**
  The same reference material is used for DS and DP.

- **Manufacturing process summary:**

(b) (4)

- **Container closure:**
  The DP container closure system is a [redacted] (b) (4) glass vial with [redacted] (b) (4) stopper, and aluminum seal with plastic flip off cap attached.

- **Dating period and storage conditions:**
  The dating period for Cimerli is 36 months when stored at 5 ± 3°C, protected from light.

- **List of co-packaged components, if applicable:** N/A

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Stored refrigerated at 2 – 8°C
- Do not freeze
- Protect from light

F. Establishment Information:

Overall recommendation: *Approve*

Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacturing, in-process, release, and stability testing of DS. WCB storage. Release and stability testing of DP. (Clarity/color, pH, osmolality, bioburden, DNA, HCP, PS-20, nrCE-SDS, SE-HPLC, CEX-HPLC, RP-HPLC, UV280)	[redacted] (b) (4)		On-site PLI	An 11-item Form FDA 483 was issued to the firm on [redacted] (b) (4)	Approve - Based on Inspection
[redacted] (b) (4)					

In-process testing; MCB/WCB manufacturing, release testing, and storage	(b) (4)	Approve - Based on Previous History	N/A	Approve - Based on Previous History
In-process and release testing of DS and DP (b) (4)		Approve - Based on Previous History	N/A	Approve - Based on Previous History
Release and stability testing of DS and DP (iLite assay)		Approve - Based on Previous History	N/A	Approve - Based on Previous History
Manufacture and visual inspection of DP. Release, stability, and in-process control testing of the DP. (Appearance, clarity, color, osmolality, pH, filling volume, CCIT)		PLI waiver	N/A	Approve- Based on waiver granted by OPMA/OBP
Release and stability testing of the DP. (sterility)		Approve - Based on Previous History	N/A	Approve - Based on Previous History
Release and stability testing of the DP. (subvisible particles)		Approve - Based on Previous History	N/A	Approve - Based on Previous History
Secondary packaging of the DP.		No evaluation necessary	N/A	N/A

G. Facilities:

(b) (4)

All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Analytical Similarity Testing Site

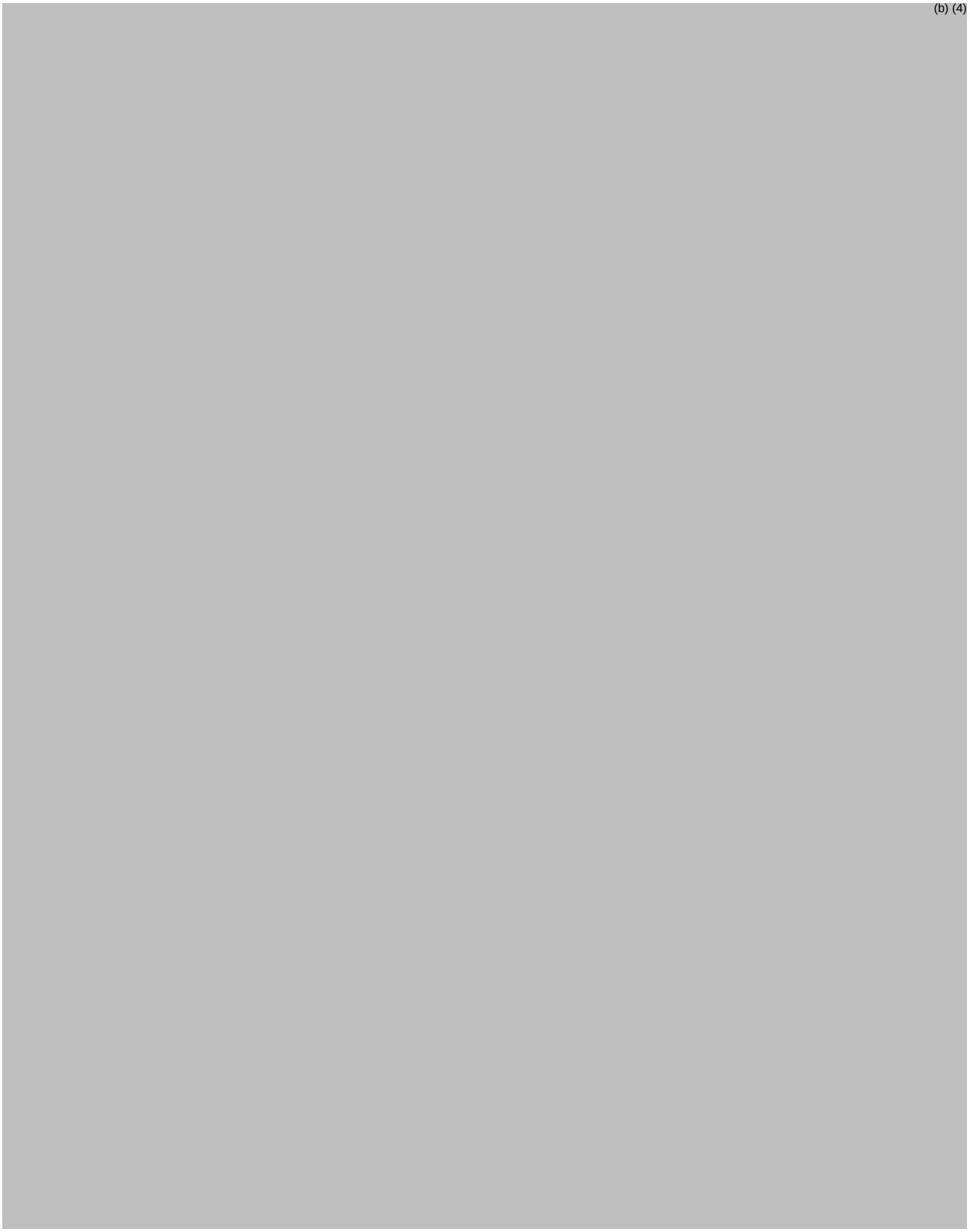
(b) (4), is the site where key comparative analytical assessment data in support of biosimilarity were collected and analyzed. A site visit was performed from (b) (4) by Drs. Jacek Cieslak (OBP) and Michael Shanks (OPMA/DBM). No objectionable observations were identified.

I. Lifecycle Knowledge Management:

i. Protocols approved:

Module	Protocol type	Proposed reporting strategy
(b) (4)		

(b) (4)



ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None identified

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/s/

LESLIE A RIVERA ROSADO
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