

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761378Orig1s000

PRODUCT QUALITY REVIEW(S)



U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	May 29, 2024
Assessor:	Liming Lu, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Odile Engel, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XV
Application:	BLA 761378
Applicant:	Formycon AG
Submission Date:	June 28, 2023 November 14, 2023
Product:	Ahzantive (afibercept-mrbb)
Dosage form(s):	Injection
Strength and Container-Closure:	2 mg/0.05 mL in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the proposed (b) (4) biosimilar product with the same dosage form, route of administration, and dosing regimen (for AMD, RVO, DME, and DR) with the vial presentation only to the reference listed drug Eylea (afibercept) injection 2 mg/0.05 mL from Regeneron Pharmaceuticals, Inc. under BLA 125387.
Recommendations:	The prescribing information, container labels, and carton labeling are acceptable from an OPQA III labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

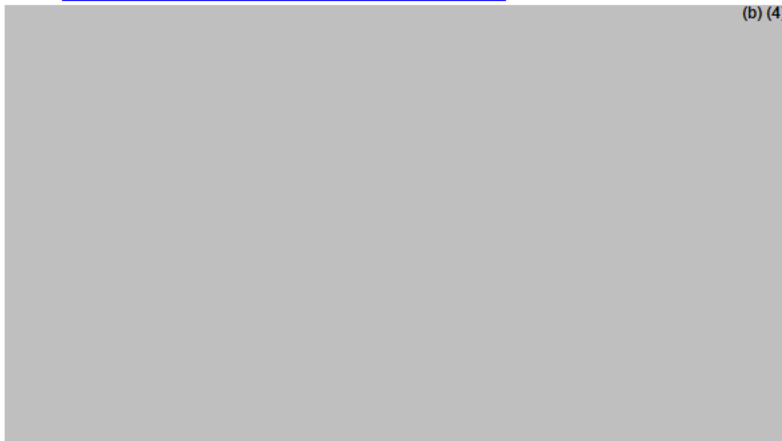
CONCLUSION

The prescribing information (submitted on May 23, 2024), container labels and carton labeling (submitted on May 23, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

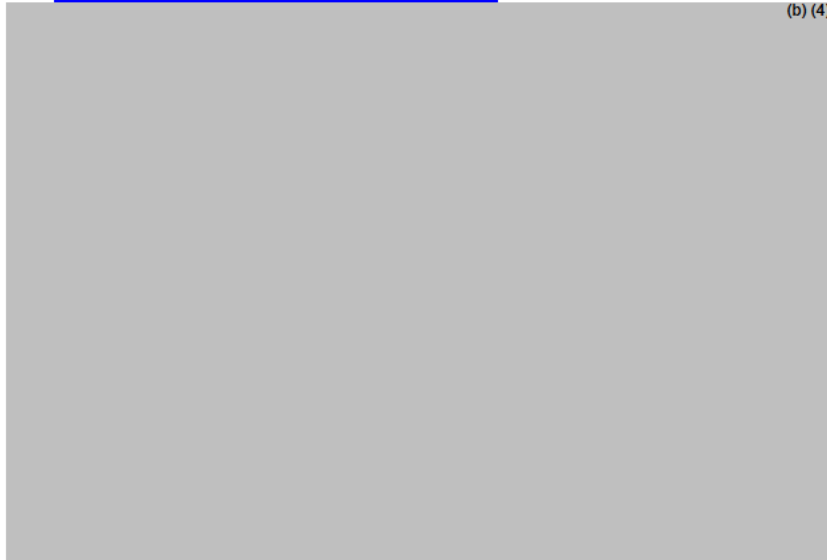
APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on June 28, 2023)
<\\CDSESUB1\EVSPROD\bla761378\0001\m1\us\114-labeling\draft\labeling\prescribing-information-word-clean.docx>
- Container Labels (submitted on June 28, 2023 and November 14, 2023)
<\\CDSESUB1\EVSPROD\bla761378\0001\m1\us\114-labeling\draft\carton-and-container\vial-label-2mg005ml.pdf>



<\\CDSESUB1\EVSPROD\bla761378\0011\m1\us\114-labeling\draft\carton-and-container\vial-label-2mg005ml.pdf>



- Carton Labeling (submitted on June 28, 2023 and November 14, 2023)
<\\CDSESUB1\EVSPROD\bla761378\0001\m1\us\114-labeling\draft\carton-and-container\carton-label-2mg005ml.pdf>

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i), 21 CFR 600.3(k)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, the qualifying phrase "Manufactured by" is not required per 21 CFR 610.60(c).

Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022) USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The product does not need a Medication Guide. Also, the label is small and would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).

No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The container is enclosed in a package.

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The product contains a container label.

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.

The applicant has confirmed there is no text on the ferrule and cap overseal of the vials.

Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

The applicant has confirmed that approximately 4 mm of the vial's circumference remains uncovered by the label, ensuring sufficient area for visual inspection. Additionally, the label is transparent, which further facilitates visual inspection of the vial's contents.

Route of administration (container label)	Acceptable
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the route of administration "for intravitreal use" to the container label per 21 CFR 201.5 (f) and to appear after the strength statement.

The applicant has revised as requested.

NDC numbers (container label)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (container label)	Acceptable
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Package type term (container label)	Acceptable
<i>Recommended labeling practices: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

No misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011)</i> <i>Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required. See carton comments.

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package⁶ Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2), 21 CFR 600.3(k)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Recommend revising the country of origin labeling statement from (b) (4) to appear as "Product of U.S.A."

The applicant has revised as requested.

Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	☒ Yes ☐ No ☐ N/A

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

⁶ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Preservative (package labeling)	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters: <7> Labeling</i>	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: <i>The carton labeling submitted by the applicant presented the product strength as (b) (4) which followed recommended labeling practices for injectable products with less than 1 mL volume. The Applicant revised the product strength to "2 mg (0.05 mL of a 40 mg/mL solution)" on the carton to be consistent with the product strength in the reference product Eylea's current label/labeling (BLA 125387/S84 approved on December 14, 2023, as recommended by the Division of Ophthalmology (DO) for improved clarity). We defer to DMEPA for medication error concerns related to the presentation of the product strength. We note that this label meets the regulatory requirements for quantitative amount of active ingredient, but does not conform to the consistent approach for FDA approved labeling that follows USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) for labeling of injectable products which states that "For single-dose and multiple-dose injectable drug products with container that supply a volume of drug less than 1 mL: the only expression of strength should be strength per fraction of mL". The presentation of strength for intravitreal injectable products is under policy discussion to appear as DO proposes.</i>	
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Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: We refer to your Description and Composition of the Drug Product submitted to BLA section 3.2.P.1 on June 28, 2023. We are evaluating the submission to ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and excipients). According to your 3.2.P.1 submission, (b) (4)

(b) (4)

(b) (4) The approved labeling should use the inactive ingredient established name (USP monograph title) "histidine" and the common or usual name can be used to present L-histidine hydrochloride monohydrate. Per 21 CFR

201.100(b)(5)(iii), the labeling must bear the quantity or proportion of all inactive ingredients. We ask that you revise the ingredient information to provide the individual excipient names and amounts that are being added to the formulation, which should be histidine and L-histidine hydrochloride monohydrate in "mg" that (b) (4) per your 3.2.P.1 submission. **Please confirm you agree with this revision.**

We also recommend revising the presentation of the inactive ingredients to have the quantitative amounts of the active ingredients appear in front of the name and the quantitative amounts of the inactive ingredients appear in "mg" after the name in parenthesis to differentiate the actives from inactives.

In addition, we have also revised the inactive ingredients list in alphabetical order according to USP General Chapters <1091> Labeling of Inactive Ingredients.

The inactive ingredients on the carton labeling should read as:

"Each single-dose vial is designed to deliver 0.05 mL (50 microliters) of 40 mg/mL aflibercept-mrbb aqueous solution with histidine (0.046 mg), L-histidine hydrochloride monohydrate (0.043 mg), polysorbate 20 (0.015 mg), sodium chloride (0.117 mg), and sucrose (2.5 mg), pH 6.2".

The applicant has revised as requested.

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(r)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with Product Quality Assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for **aflibercept** products (i.e., there is no specific test method described in regulation for **aflibercept** products that establishes an official standard of potency) and 2) Product Quality Assessors have determined that potency is not a factor within the meaning of § 610.61(r) for **Ahzantive** because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A
Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A
Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A
Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	☒ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) <i>USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Package type term (package labeling)	Acceptable
<i>Recommended labeling practices: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use</i> (October 2018) <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

No misleading statements (package labeling)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Prominence of required label statements (package labeling)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain phenylalanine.

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain sulfites.

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise Statement of Dosage to read "Dosage: See prescribing information." to be in alignment with PLR labeling format. <i>The applicant has revised as requested.</i>

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
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Comment/Recommendation: We revised the dosage form "injection" in the product title to appear in all lowercase letters as recommended in the Draft Guidance *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format* (January 2018).

The applicant has revised as requested.

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: *The proposed prescribing information (USPI) submitted by the applicant presented the product strength as (b) (4) which followed recommended labeling practices for injectable products with less than 1 mL volume. The Applicant revised the product strength to "2 mg (0.05 mL of a 40 mg/mL solution)" throughout the labeling to be consistent with the product strength in the reference product Eylea's current USPI (BLA 125387/S84 approved on December 14, 2023, as recommended by the Division of Ophthalmology (DO) for improved clarity). We defer to DMEPA for medication error concerns related to the presentation of the product strength. We note that this label meets the regulatory requirements for quantitative amount of active ingredient, but does not conform to the consistent approach for FDA approved labeling that follows USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) for labeling of injectable products which states that "For single-dose and multiple-dose injectable drug products with container that supply a volume of drug less than 1 mL: the only expression of strength should be strength per fraction of mL". The*

presentation of strength for intravitreal injectable products is under policy discussion to appear as DO proposes.

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv) <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i>	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i> <i>Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2023)</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: We revised the filter needle information to "18-gauge" based on the evaluation of submitted data.

A 5-micron sterile filter needle (b) (4) 18-gauge × 1½-inch), a 1-mL sterile Luer lock syringe and a 30-gauge × ½-inch sterile injection needle are needed, but not provided.

We revised this to read as "...glass vial is for one-time use in one eye only." for clarity and to mitigate confusion with the (b) (4)

We also recommended including the statement "Discard unused portion." for single-dose injectable drug products.

The applicant has revised as requested.

We previously had a comment to the applicant to revise to the required verbatim statement for parenterals per 21 CFR 201.57(c)(3)(iv) in section 2. This recommendation was not implemented by the Division of Ophthalmology (DO) because ophthalmic products are not considered to be parenterals. We also note this required verbatim statement has not been implemented in the reference product Eylea's prescribing information. We defer to DO for the final recommendation to the applicant regarding the required verbatim in the applicable section.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: The proposed prescribing information (USPI) submitted by the applicant presented the product strength as (b) (4) which followed recommended labeling practices for injectable products with less than 1 mL volume. The Applicant revised the product strength to "2 mg (0.05 mL of a 40 mg/mL solution)" throughout the labeling to be consistent with the product strength in the reference product Eylea's current USPI (BLA 125387/S84 approved on December 14, 2023, as recommended by the Division of Ophthalmology (DO) for improved clarity). We defer to DMEPA for medication error concerns related to the presentation of the product strength. We note that this product meets the regulatory requirements for quantitative amount of active ingredient, but does not conform to the consistent approach for FDA approved labeling that follows USP General Chapters <7> Labeling (Strength per total volume for single dose and multiple dose injectable drug products) for labeling of injectable products which states that "For single-dose and multiple-dose injectable drug products with container that supply a volume of drug less than 1 mL: the only expression of strength should be strength per fraction of mL". The presentation of strength for intravitreal injectable products is under policy discussion to appear as DO proposes.

Full Prescribing Information	
11 DESCRIPTION	Acceptable
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: We added the placeholder for 4-letter suffix to the proper name of drug product in the first paragraph of Section 11 in USPI because it discusses the drug substance.

We revised the statement to align with the current RP Eylea label for the preservative statement.

We refer to your Description and Composition of the Drug Product submitted to BLA section 3.2.P.1 on June 28, 2023. We are evaluating the submission to ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and excipients). According to your 3.2.P.1 submission, (b) (4)

(b) (4) The approved labeling should use the inactive ingredient established name (USP monograph title) "histidine" and the common or usual name can be used to present L-histidine hydrochloride monohydrate. Per 21 CFR 201.100(b)(5)(iii), the labeling must bear the quantity or proportion of all inactive ingredients. We ask that you revise the ingredient information to provide the individual excipient names and amounts that are being added to the formulation, which should be histidine and L-histidine hydrochloride monohydrate in "mg" that (b) (4)

(b) (4)
per your 3.2.P.1 submission. **Please confirm you agree with this revision.**

We recommend revising the presentation of the inactive ingredients to have the quantitative amounts of the active ingredients appear in front of the name and the quantitative amounts of the inactive ingredients appear in "mg" after the name in parenthesis to differentiate the actives from inactives. In addition, we have also revised the inactive ingredients list in alphabetical order according to *USP General Chapters <1091> Labeling of Inactive Ingredients*.

designed to deliver 0.05 mL (50 microliters) of solution containing 2 mg of aflibercept-mrbb in histidine (0.046 mg), L-histidine hydrochloride monohydrate (0.043 mg), polysorbate 20 (0.015 mg), sodium chloride (0.117 mg), (b) (4) sucrose (2.5 mg) and water for injection- (b) (4) with a pH of 6.2.

The applicant has revised as requested.

Full Prescribing Information	
15 & 16 Hazardous Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. ¹	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Recommend including the statement "Discard unused portion." for single-dose injectable drug products.

We recommend including the identifying characteristics "a clear, colorless to pale yellow solution" of the dosage form in section 16. The appropriate information to facilitate identification of the dosage form should be included in section 16 per 21 CFR 201.57(c)(17)(iii).

The applicant has revised as requested. The applicant has confirmed to update the NDC number once it's assigned.

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on May 23, 2024)
<\\CDSESUB1\EVSPROD\bla761378\0023\m1\us\114-labeling\draft\labeling\prescribing-information-word-clean.docx>
- Container Labels (submitted on May 23, 2024)
<\\CDSESUB1\EVSPROD\bla761378\0023\m1\us\114-labeling\draft\carton-and-container\vial-label-2mq005ml.pdf>



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BLA Executive Summary

Assessment Date: 5/8/2024

1. Application/Product Information

BLA number	761378
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351(k) (b) (4) to US-licensed Eylea (aflibercept)
Associated IND/BLA	IND 144550
Review Designation	Standard Review
Applicant	Formycon AG
Indication	Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) (Note: Due to unexpired exclusivity, Formycon AG is not seeking approval for the orphan Retinopathy of Prematurity (ROP) indication approved for US-licensed Eylea.)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: AHZANTIVE
	Non-proprietary Name/Code Name: aflibercept-mrbb
	OBP Naming: FUS: MABFRAG HUMAN (IGG1); RPROTFRAG P35968 (VGFR2_HUMAN); RPROTFRAG P17948 (VGFR1_HUMAN) [FYB203]
Drug Product Description	AHZANTIVE (aflibercept-mrbb) injection is a sterile, preservative-free, clear, and colorless to pale yellow

	solution, supplied in a single-dose glass vial designed to deliver 0.05 mL solution containing 2 mg of aflibercept-mrbb in histidine (0.046 mg), L-histidine hydrochloride monohydrate (0.043 mg), polysorbate 20 (0.015 mg), sodium chloride (0.117 mg), sucrose (2.5 mg) and water for injection with a pH of 6.2. Aflibercept-mrbb is a recombinant homodimeric fusion protein, with each chain consisting of portions of human VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2) extracellular domains fused to the Fc portion of human IgG1. The fusion protein has a total of 864 amino acids (432 amino acids per chain) and a protein molecular weight of 97 kDa. Glycosylation at five N-linked glycosylation sites, with four located in the VEGFR domain and one located in the Fc domain, constitutes an additional 15% of the molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept-mrbb is produced using recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.
Dosage Form	Solution, injection
Strength	2 mg/0.05 mL (40 mg/mL) solution in a single-dose vial
Route of Administration	Intravitreal injection
Primary Container Closure System	(b) (4) glass vial, closed with a (b) (4) stopper with (b) (4) and sealed by an aluminum seal with a plastic flip-off cap
Device Information	Not applicable (Note: US-licensed Eylea also has a 2 mg/0.05 mL single-dose prefilled syringe presentation. Formycon AG

	is not seeking approval for the prefilled syringe presentation.)		
Co-packaged Product Information	Not applicable (Note: US-licensed Eylea vial presentation is co-packaged with the following device components: (1) one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents, (2) one 30-gauge x ½-inch injection needle for intravitreal injection, and (3) one 1-mL syringe for administration. AHZANTIVE (aflibercept-mrbb) does not include these co-packaged device components.)		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Mercy Oyugi	Nailing Zhang
	Drug product	Odile Engel	
	Comparative Analytical Assessment (CAA), Immunogenicity Assay	Dilip Devineni	
	Facility	Jiangsong Jiang (DS) / Yi Wang (DP)	Michael Shanks
	Microbiology	Jiangsong Jiang (DS) / Yi Wang (DP)	Madushini Dharmasena
	RBPM	Shazma Aftab	
	ATL	Nailing Zhang	
	Review Chief	Maria-Teresa Gutierrez-Lugo	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761378 for AHZANTIVE (aflibercept-mrbb) manufactured by Formycon AG. The data submitted in this application are adequate to support the conclusion that the manufacture of AHZANTIVE (aflibercept-mrbb) is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that AHZANTIVE (aflibercept-mrbb) is highly similar to US-licensed Eylea (aflibercept), notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** (b) (4)
(b) (4)
- **Drug Product:**
 - Manufacturing: (b) (4)
(b) (4)
 - Labeling and secondary packaging: (b) (4)
(b) (4)

b. Fill size and dosage form:

- 2 mg/0.05 mL (40 mg/mL) solution in a single-dose vial

c. Dating Period:

- **Drug Substance:** (b) (4)
- **Drug Product:** 24 months at 2°C - 8°C, protected from light
- **Stability Option:**
 - For stability protocols:
 - 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
- AHZANTIVE is exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

AHZANTIVE (aflibercept-mrbb) is (b) (4) to US-licensed Eylea (aflibercept) for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR). Aflibercept is a recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1. It acts as a soluble decoy receptor that binds VEGF-A and Placental Growth Factor (PlGF), and thereby can inhibit the binding and activation of the VEGF receptors. Potency of AHZANTIVE (aflibercept-mrbb) is controlled using a cell-based reporter assay that measures its ability to inhibit VEGF-A-induced luciferase reporter activity in iLite VEGF cell line, a stably transfected HEK-239 cell line expressing VEGFR-2 together with GAL4-Elk1a responsive luciferase gene. Potency results are reported as percentage relative to a qualified reference material.

The totality of the comparative analytical evidence supports that AHZANTIVE (aflibercept-mrbb) is highly similar to US-licensed Eylea (aflibercept), notwithstanding minor differences in clinically inactive components. The strength of 2 mg/0.05 mL (40 mg/mL) AHZANTIVE in a single-dose vial demonstrated the same strength as that of US-licensed Eylea. Refer to [Appendix](#) for detailed summary on comparative analytical assessment.

The drug substance (DS) manufacturing process consists of (b) (4)

(b) (4)

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. All facilities used for the manufacture and quality control testing were found acceptable for the

proposed operations. On-site pre-licensing inspections (PLIs) for the DS manufacturing facility (b) (4) and the DP manufacturing facility (b) (4) were conducted in (b) (4) and (b) (4) respectively. Both PLIs were classified as "Voluntary Action Indicated (VAI)", and the responses to FDA Form 483 were reviewed and found satisfactory.

The overall AHZANTIVE (aflibercept-mrbb) 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 AHZANTIVE (aflibercept-mrbb) 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. The BLA is recommended for approval from the product quality, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
CAA	-	Adequate
Immunogenicity Assay	-	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 AHZANTIVE (i.e., there is no specific test method described in regulation for AHZANTIVE that establishes an official standard of potency). We next considered whether potency is a factor for AHZANTIVE 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 AHZANTIVE for purposes of § 610.61(r) because lot variability is not a concern for AHZANTIVE as AHZANTIVE's 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: None

c. Drug Product:

i. Protocols approved:

- Qualification protocol for commercial drug product shipping
- Stability protocols for drug product shelf-life extension
- Post-approval stability protocols for drug product

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.

For use with OPQ-OBP-SOP-3104: OPQ-OBP-TEM-0010-07 [BLA Executive Summary Template Non-annotated]

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

U.S.-licensed Eylea (hereafter referred to as US-Eylea) is available in one strength with two presentations: (1) 2 mg/0.05 mL (40 mg/mL) solution in a single-dose pre-filled syringe, and (2) 2 mg/0.05 mL (40 mg/mL) solution in a single-dose vial co-packaged with injection components (filter needle, syringe, and injection needle). Formycon AG is currently seeking approval of 2 mg/0.05 mL FYB203 as a (b) (4) biosimilar for the vial presentation only, without co-packaged injection components.

The Comparative Analytical Assessment (CAA) between FYB203, US-Eylea, and E.U.-approved Eylea (hereafter referred to as EU-Eylea) compared a total of 8 independent FYB203 lots (including 7 drug product (DP) lots and 1 drug substance (DS) lot), 16 US-Eylea lots (vial), and 22 EU-Eylea lots (vial). The eight independent FYB203 lots were manufactured between June 2019 and December 2022 using the (b) (4) L scale clinical and commercial processes, and included two clinical DP lots, two PPQ DP lots, and one PPQ DS lot that was not forward processed to DP. It is acceptable to include one FYB203 DS lot in the CAA as the DS and DP formulations are identical. The expiry dates of 16 US-Eylea lots ranged from May 2016 to December 2022, and the expiry dates of 22 EU-Eylea lots ranged from December 2015 to June 2023. US-Eylea and EU-Eylea lots were generally analyzed shortly after sourcing. If an immediate measurement was not possible, they were analyzed within their shelf-life or were frozen prior to the expiry date. A freeze-thaw study confirmed that the samples were not affected by the freeze-thaw procedure. The lots were adequate to capture potential lot-to-lot variability in the US-Eylea and EU-Eylea products over time.

An extensive comparative physiochemical and functional assessment of the quality attributes of FYB203, US-Eylea, and EU-Eylea was performed, which included comparisons of primary structure, higher order structure, post-translational modifications, product-related size and charge variants, glycosylation, protein concentration, and biological properties (Table A). Quality attributes were selected and ranked by criticality and current knowledge of the mechanism(s) of action, and were assessed accordingly by quantitative and qualitative approaches. Orthogonal methods were implemented and were designed to be capable of detecting analytical differences between the products if present. Results from method validation or qualification studies support the suitability of the methods used in the CAA.

The Applicant used an acceptable risk-based approach for statistical evaluation of analytical results. The quality range method was employed for the analysis of high and moderate risk quality attributes using quality ranges obtained from US-Eylea and/or EU-Eylea lots to account for manufacturing variability and assay variability. Attributes tested using quantitative assays that are not amenable to statistical analysis and

qualitative assays were evaluated using visual comparisons. The data evaluation methods used were consistent with the FDA draft guidance for industry *Development of Therapeutic Protein Biosimilar: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019).

The CAA also included comparative stability studies under accelerated, freeze-thaw, and forced degradation conditions including thermal stress, agitation stress, photo stress, oxidation stress, low and high pH, and glycation stress, to demonstrate that FYB203 has a similar degradation profile to that of US-Eylea and EU-Eylea.

In conclusion, the FYB203 and US-Eylea data support a demonstration that FYB203 is highly similar to US-Eylea, notwithstanding minor differences in clinically inactive components. FYB203 has the same strength and dosage form for the intravitreal route of administration as US-Eylea. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate quality attributes of FYB203 and US-Eylea to support the demonstration that the products are highly similar. The numbers of lots tested were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While differences were observed in a limited number of attributes, these differences do not preclude a demonstration that FYB203 is highly similar to US-Eylea.

In addition, three-way pairwise analytical comparisons of FYB203, US-Eylea, and EU-Eylea were used to establish the scientific bridge between FYB203, US-Eylea, and EU-Eylea. Based on the assessment of the analytical data, the Applicant established the scientific bridge between FYB203, US-Eylea, and EU-Eylea, using the same methods and statistical approaches as those to support a demonstration that FYB203 is highly similar to US-Eylea. Based on review of the data, the scientific bridge was established to support the relevance of the data generated from clinical studies using EU-Eylea as the comparator for the assessment of biosimilarity.

B. Results of Comparative Analytical Assessment

The results of the analytical comparisons support a demonstration that FYB203 is highly similar to US-Eylea and the establishment of the scientific bridge between FYB203, US-Eylea and EU-Eylea. The results are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physicochemical / Functional Characteristics	Quality Attribute Assessed (Analytical Methods)	Supports a Demonstration of Highly Similar	Supports the Scientific Bridge
--	---	--	--------------------------------

Primary structure	Amino acid sequence (LC-MS/MS sequencing and Edman degradation)	Yes	Yes
	Molecular weight (intact mass deglycosylated) (LC-MS)	Yes	Yes
Higher order structure	Disulfide bonds (LC-MS/LC-UV peptide map non-reduced, Ellman's assay)	Yes	Yes
	Secondary structure (FTIR, Far-UV CD)	Yes	Yes
	Tertiary structure (Near-UV CD)	Yes	Yes
	Thermodynamic stability (nanoDSF)	Yes	Yes
Post-translational modifications	Oxidation Met20, Met163, Met192, Met237*, Trp298, Met413 (LC-MS/MS peptide mapping reduced)	Yes	Yes
	Deamidation Asn84*, Asn99*, Asn152 (LC-MS/MS peptide mapping reduced)	Yes	Yes
	C-terminal Lys clipping (LC-MS/MS peptide mapping reduced)	Yes	Yes
	C-terminal Pro amidation* (LC-MS/MS peptide mapping reduced)	Yes	Yes
	Isoaspartate (IsoAsp)* (RP-HPLC)	Yes	Yes
	Glycation (Fc domain, VEGFR domain) (LC-MS subunit mass)	Yes	Yes
Product-related substances / impurities (size variants)	Purity (monomer) (SV-AUC, SE-HPLC*)	Yes	Yes
	Aggregates / HMW Species (SV-AUC*, SE-HPLC*)	Yes	Yes
	Purity (main species) (rCE-SDS*, nrSDS-PAGE)	Yes	Yes
	Fragments / LMW species (rCE-SDS*, nrSDS-PAGE)	Yes	Yes
Product-related substances / impurities (charge variants)	Main peaks (icIEF-native*, icIEF-asialo (desialylated)*)	Yes	Yes
	Acidic peaks (icIEF-native*, icIEF-asialo (desialylated)*)	Yes	Yes
	Basic peaks (icIEF-native*, icIEF-asialo (desialylated))	Yes	Yes
Glycosylation	Mannosylation (whole molecule*, Fc domain, VEGFR domain*) (RapiFluor HILIC-HPLC)	Yes	Yes

	Afucosylation (whole molecule*, Fc domain*, VEGFR domain*) (RapiFluor HILIC-HPLC)	Yes	Yes
	Galactosylation (whole molecule, Fc domain*, VEGFR domain) (RapiFluor HILIC-HPLC)	Yes	Yes
	Sialylation (sum of whole molecule*, whole molecule mono-sialylated*, whole molecule di-sialylated, whole molecule tri-sialylated*) (RapiFluor HILIC-HPLC)	Yes	Yes
	Sialylation (sum of Fc domain) (RapiFluor HILIC-HPLC)	Yes	Yes
	Sialylation (sum of VEGFR domain*, VEGFR domain mono-sialylated*, VEGFR domain di-sialylated*, VEGFR domain tri-sialylated*) (RapiFluor HILIC-HPLC)	Yes	Yes
	Glycosylation site occupancy Asn68* (LC-MS/MS peptide mapping reduced)	Yes	Yes
Biological activity	VEGF-A165 binding and neutralization (iLite cell-based potency assay, HUVEC cell proliferation assay, relative potency ELISA, binding kinetics BLI)	Yes	Yes
	VEGF-A121 binding (relative potency ELISA)	Yes	Yes
	VEGF-A189 binding (relative potency ELISA)	Yes	Yes
	VEGF-B binding (VEGF-B186 relative potency ELISA)	Yes	Yes
	PIGF binding (PIGF-2 relative potency ELISA, PIGF-2 binding kinetics SPR, PIGF-1 relative potency ELISA)	Yes	Yes
	Galectin-1 binding (ELISA)	Yes	Yes
	VEGF-C binding (BLI)	Yes	Yes
	VEGF-D binding (ELISA)	Yes	Yes
Additional biological	FcRn binding (binding kinetics BLI)	Yes	Yes
	FcγRI binding (binding kinetics SPR)	Yes	Yes

properties	FcγRIIIA (158V, 158F) binding* (binding kinetics SPR)	Yes	Yes
	C1q binding (ELISA)	Yes	Yes
	ADCC activity (cell-based assay)	Yes	Yes
	CDC activity (cell-based assay)	Yes	Yes
General properties	Protein concentration (UV280)	Yes	Yes
Stability profiles	Accelerated (b) (4)	Yes	Yes
	Freeze-thaw (b) (4)	Yes	Yes
	Thermal stress (b) (4)	Yes	Yes
	Agitation stress (b) (4)	Yes	Yes
	Photo stress (b) (4)	Yes	Yes
	Oxidation stress (b) (4)	Yes	Yes
	Low and high pH (b) (4)	Yes	Yes
	Glycation stress (b) (4)	Yes	Yes

*: See Section D.

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

A comparative clinical study (Protocol# FYB203-03-01) was conducted for the clinical development of FYB203, comparing FYB203 and EU-Eylea in patients with neovascular AMD. The title of the clinical study protocol is: "A Phase 3 Randomized, Double-masked, Multicenter Study to Compare the Efficacy and Safety of the Proposed Aflibercept FYB203 Biosimilar in Comparison to Eylea in Patients with Neovascular Age-Related Macular Degeneration (MAGELLAN-AMD)". Two FYB203 clinical DP lots and seven EU-Eylea lots (vial) were used in the clinical study, and were also included in the CAA study (see Section A above).

To support the relevance of clinical data generated using EU-Eylea as a comparator product for the assessment of biosimilarity, the Applicant performed three-way, pairwise comparative analytical assessments, which included comparison of FYB203 to US-Eylea, FYB203 to EU-Eylea, and US-Eylea to EU-Eylea. The same analytical methods

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used for supporting a demonstration that FYB203 is highly similar to US-Eylea were used for the pairwise comparisons with EU-Eylea. The differences observed in the comparative analytical studies do not preclude the establishment of the scientific bridge (see Section D below). The results support the establishment of the scientific bridge between FYB203, US-Eylea, and EU-Eylea.

D. Assessment of Comparative Analytical Study Results

Several quality attributes did not meet the pre-determined similarity acceptance criteria (i.e., at least 90% of FYB203 lots must be within the quality range) or showed variable results in qualitative assessments (Table 9, Section 3.2.R *Analytical Similarity Assessment*); however, adequate justification has been provided that the differences observed do not preclude a demonstration that FYB203 is highly similar to US-Eylea, or the establishment of the scientific bridge between FYB203, US-Eylea, and EU-Eylea. These instances are described below. Note that all ranges for FYB203 lots listed below are min - max ranges, while all ranges for US-Eylea and EU-Eylea lots are quality ranges (mean $\pm$ 3SD).

Oxidation

Oxidation at Met20, Met163, Met192, Met237, Trp298 and Met413 were evaluated by LC-MS/MS reduced peptide mapping. The level of oxidation at Met237 was lower in FYB203 lots (1.7 – 2.8%) compared to US-Eylea lots (3.4 – 5.7%) and EU-Eylea lots (3.1 – 6.5%). Met237 oxidation levels are similar between US-Eylea lots and EU-Eylea lots. Met237 is located at the FcRn binding site in the Fc domain, and oxidation at this site may have an impact on FcRn binding and subsequently PK. However, considering that Met237 oxidation was very low in FYB203, US-Eylea and EU-Eylea, and that no differences were detected in the FcRn binding assay between FYB203, US-Eylea and EU-Eylea, this difference is not anticipated to have a clinical impact. Based on the foregoing, it is considered acceptable and does not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

Deamidation

Deamidation at Asn84, Asn99 and Asn152 were evaluated by LC-MS/MS reduced peptide mapping. The level of deamidation at Asn84 was lower in FYB203 lots (7.9 – 11.2%) compared to US-Eylea lots (15.9 – 33.0%) and EU-Eylea lots (20.6 – 30.8%). The level of deamidation at Asn99 was also slightly lower in FYB203 lots (1.7 – 2.9%) compared to US-Eylea lots (2.2 – 6.9%) and EU-Eylea lots (3.1 – 6.1%). Asn84 and Asn99 deamidation levels are similar between US-Eylea lots and EU-Eylea lots. Although Asn84 and Asn99 are located in the VEGFR domain, these sites are not in the immediate vicinity of the target binding sites. Furthermore, no influence on potency was detected even for increased levels of deamidation as shown in forced degradation

studies. Therefore, the differences in Asn84 and Asn99 deamidations are considered acceptable and do not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

C-terminal Pro amidation

C-terminal Pro430 amidation was evaluated by LC-MS/MS reduced peptide mapping. The level of C-terminal Pro430 amidation was lower in FYB203 lots (0 – 0.1%) compared to US-Eylea lots (0.9 – 2.4%) and EU-Eylea lots (0.6 – 2.4%). C-terminal Pro430 amidation levels are similar between US-Eylea lots and EU-Eylea lots. This quality attribute is generally recognized as low risk for clinical impact. In addition, considering that Pro430 amidation level is very low in FYB203, US-Eylea and EU-Eylea, and that C-terminal proline amidation does not affect antigen binding according to the CQA assessment, this difference is considered acceptable and does not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

Isoaspartate (IsoAsp)

The overall level of isoaspartate (IsoAsp; can be formed by Asn deamidation or Asp isomerization) was quantified by RP-HPLC. IsoAsp level was lower in FYB203 lots (0.14 – 0.20 mol/mol) compared to US-Eylea lots (0.32 – 0.52 mol/mol) and EU-Eylea lots (0.34 – 0.49 mol/mol). The overall IsoAsp levels are similar between US-Eylea lots and EU-Eylea lots. IsoAsp in the VEGFR domain could potentially impact target binding and subsequently potency, while IsoAsp in the Fc domain could potentially impact FcRn binding and subsequently PK; impact on immunogenicity cannot be excluded, either. However, considering that IsoAsp level was very low in FYB203, US-Eylea and EU-Eylea, and that no relevant differences were observed in multiple potency assays or in the FcRn binding assay between FYB203, US-Eylea and EU-Eylea, this minor difference is not anticipated to have a clinical impact. Based on the foregoing, it is considered acceptable and does not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

Purity (monomer) and HMW species

Purity (monomer) and HMW species were evaluated by SE-HPLC and SV-AUC. The SE-HPLC method showed that FYB203 had higher level of monomer (99.31 – 99.77%) compared to US-Eylea (97.65 – 98.89%) and EU-Eylea (97.36 – 99.32%), and lower level of HMW species (0.23 – 0.69%) compared to US-Eylea (1.11 – 2.35%) and EU-Eylea (0.68 – 2.64%). The orthogonal SV-AUC method also showed that FYB203 had lower level of HMW species ($\leq$ LOQ) compared to US-Eylea (0.8 – 2.9%) and EU-Eylea (1.0 – 3.1%). The levels of monomer and HMW species are similar between US-Eylea lots and EU-Eylea lots. The difference in HMW species is not anticipated to have a

clinical impact given the low levels of HMW species and the magnitude of the difference. As evidence of this, FYB203, US-Eylea and EU-Eylea are similar with respect to biological activity in multiple potency assays. Therefore, the differences in monomer and HMW species are considered acceptable and do not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

Purity (main species) and LMW species

Purity (main species) and LMW species were evaluated by reduced CE-SDS as the leading method. FYB203 had higher level of main species (97.74 – 98.42%) compared to US-Eylea (92.59 – 95.54%) and EU-Eylea (91.77 – 96.15%), and lower level of LMW species (1.58 – 2.26%) compared to US-Eylea (4.46 – 7.41%) and EU-Eylea (3.85 – 8.23%). The levels of main species and LMW species are similar between US-Eylea lots and EU-Eylea lots. The difference in LMW species is not anticipated to have a clinical impact given the low levels of LMW species and the magnitude of the difference. As evidence of this, FYB203, US-Eylea and EU-Eylea are similar with respect to biological activity in multiple potency assays. Therefore, the differences in main species and LMW species are considered acceptable and do not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

Charge variants

Aflibercept is highly sialylated within the VEGFR domain; therefore, charge profiles were evaluated by both icIEF-native and icIEF-asialo (desialylated; after sialidase digest). The icIEF-native method showed that FYB203 had slightly lower level of main peaks (60.31 – 65.95%) compared to US-Eylea (64.11 – 71.55%) and EU-Eylea (62.83 – 72.79%), slightly lower level of acidic peaks (10.21 – 21.75%) compared to US-Eylea (14.42 – 21.31%) and EU-Eylea (14.83 – 20.69%), and slightly higher level of basic peaks (12.29 – 29.48%) compared to US-Eylea (9.08 – 19.54%) and EU-Eylea (7.89 – 20.97%). After treated with sialidase, the icIEF-asialo method showed that FYB203 had higher level of main peaks (71.47 – 74.58%) compared to US-Eylea (60.23 – 70.78%) and EU-Eylea (60.92 – 69.89%), and slightly lower level of acidic peaks (21.74 – 25.77%) compared to US-Eylea (25.14 – 37.77%) and EU-Eylea (25.87 – 37.21%); the level of basic peaks in FYB203 (2.33 – 4.07%) was within the quality ranges of US-Eylea (1.14 – 4.95%) and EU-Eylea (0.99 – 5.11%). The levels of main peaks, acidic peaks and basic peaks measured by both icIEF-native and icIEF-asialo are similar between US-Eylea lots and EU-Eylea lots. It appears that slight differences in sialylation (see Glycosylation section below for more discussion) may have a strong impact on the charge profile. After sialidase treatment to remove the main contributing factor (i.e., sialylation), a shift to a more basic charge profile was observed. The lower level of deamidation, which is also shown to contribute to charge heterogeneity by charge variant fractionation studies, observed in FYB203 compared to US-Eylea and EU-Eylea (see Deamidation section above) is likely responsible for the lower amount of acidic

peaks in FYB203 and consequently the higher level of main peaks. Considering that no relevant differences were observed in multiple potency assays or in the FcRn binding assay between FYB203, US-Eylea, and EU-Eylea, the observed differences in the charge profile are considered acceptable and do not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

Glycosylation

Aflibercept has five N-glycosylation sites on each polypeptide chain, Asn36, Asn68, Asn123, Asn196 in the VEGFR domain, and Asn282 in the Fc domain, resulting in a complex N-glycan profile. Glycosylation was evaluated by RapiFluor HILIC-UPLC N-glycan profiling. While the N-glycan profiles are similar between US-Eylea and EU-Eylea lots, FYB203 had a slightly different N-glycan profile with the following differences observed: (1) Mannosylation. FYB203 had a lower overall mannosylation level (3.6 – 4.5%) compared to US-Eylea (7.6 – 11.0%) and EU-Eylea (8.3 – 10.6%), and a lower mannosylation level in the VEGFR domain (5.0 – 5.6%) compared to US-Eylea (10.3 – 13.6%) and EU-Eylea (10.0 – 14.1%). (2) Afucosylation. FYB203 had a lower overall afucosylation level (36.0 – 37.9%) compared to US-Eylea (39.5 – 44.1%) and EU-Eylea (40.3 – 43.0%), a lower afucosylation level in the Fc domain (6.6 – 7.8%) compared to US-Eylea (14.8 – 17.8%) and EU-Eylea (12.1 – 18.6%), and a lower afucosylation level in the VEGFR domain (46.5 – 46.9%) compared to US-Eylea (47.6 – 52.7%) and EU-Eylea (48.3 – 51.4%). (3) Galactosylation. FYB203 had a lower galactosylation level in the Fc domain (52.3 – 53.4%) compared to US-Eylea (59.0 – 65.9%) and EU-Eylea (59.5 – 64.0%). (4) Sialylation. FYB203 had a lower overall sum sialylation level (56.2 – 61.9%) compared to US-Eylea (59.5 – 66.0%) and EU-Eylea (58.5 – 66.6%), and a lower sum sialylation level in the VEGFR domain (74.8 – 81.7%) compared to US-Eylea (80.7 – 83.7%) and EU-Eylea (78.1 – 85.4%). The differences were mainly contributed by mono-sialylation and tri-sialylation. (5) Glycosylation site occupancy at Asn68. FYB203 had a higher Asn68 glycosylation occupancy (47.3 – 51.0%) compared to US-Eylea (24.7 – 47.0%) and EU-Eylea (29.2 – 45.5%).

The glycosylation differences were assessed for their potential impacts on target binding, PK, and effector function. First, glycosylation in the VEGFR domain has no impact on target binding and was confirmed in multiple functional assays. The charge variant fractionation experiments using free-flow electrophoresis showed that fractions differing in their glycosylation profile were highly comparable in potency. The desialylated FYB203 also displayed no changes in neutralization of its targets. Second, glycosylation differences may impact binding to the mannose receptor and asialoglycoprotein receptor (ASGPR) and consequently impact PK. However, aflibercept products are injected directly into the eye and ocular PK is driven mainly by protein size

as the ASGPR is primarily expressed on hepatocytes¹. Finally, as effector function is not a known mechanism of action for aflibercept, and ADCC and CDC activities were not detected in FYB203, US-Eylea and EU-Eylea in cell-based assays, differences known to affect effector function (e.g., afucose levels) are not expected to translate into any biological effects. Therefore, the observed differences in the N-glycan profiles are considered acceptable and do not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

FcγRIIIA (158V, 158F) binding

FcγRIIIA (158V) and FcγRIIIA (158F) binding kinetics were evaluated by SPR. The relative affinity to FcγRIIIA (158V) was lower in FYB203 lots (77.3 – 94.7%) compared to US-Eylea lots (130.5 – 177.2%) and EU-Eylea lots (105.1 – 221.2%). The relative affinity to FcγRIIIA (158F) was also lower in FYB203 lots (87.7 – 94.6%) compared to US-Eylea lots (114.9 – 212.8%) and EU-Eylea lots (121.7 – 146.1%). The relative affinities to FcγRIIIA (158V) are similar between US-Eylea lots and EU-Eylea lots. The relative affinity to FcγRIIIA (158F) is higher in US-Eylea lots than in EU-Eylea lots. Lower afucosylation level in FYB203 compared to US-Eylea and EU-Eylea (see Glycosylation section above) is likely responsible for the decreased FcγRIIIA binding affinity in FYB203. Divergent levels of Fc-mediated FcγRIIIA binding could potentially impact ADCC activity and safety. However, the observed differences are not anticipated to have a clinical impact, as ADCC is not a known mechanism of action for aflibercept products, and ADCC activity was not detected in FYB203, US-Eylea and EU-Eylea in the cell-based assay. Furthermore, FYB203 showed lower binding affinity to FcγRIIIA compared to US-Eylea and EU-Eylea, which supports no increased risk of adverse effects related to immune reactions caused by binding to FcγRIIIA in the eye. Overall, the differences in FcγRIIIA (158V) and FcγRIIIA (158F) binding are considered acceptable and do not preclude a demonstration that FYB203 is highly similar to US-Eylea or the establishment of the scientific bridge.

E. Same Strength

FYB203 has the same dosage form and route of administration as US-Eylea. Formycon AG is seeking approval of 2 mg/0.05 mL FYB203 in a single-dose vial. US-Eylea is available at this strength (2 mg/0.05 mL, 40 mg/mL) in a single-dose vial co-packaged with injection components (filter needle, syringe, and injection needle)². Comparative protein concentration (mg/mL) was assessed as part of the CAA. The deliverable volume and fill weight data were also assessed in the context of manufacturing control. Based on the comparative protein concentration data and manufacturing data, FYB203

¹ D'Souza AA and Devarajan PV, 2015. [Asialoglycoprotein receptor mediated hepatocyte targeting - strategies and applications](#). *J Control Release*, Apr 10;203:126-39.

² U.S. Prescribing Information, US-licensed Eylea. Access March 1, 2024 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s084lbl.pdf

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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 US-Eylea. The strength of 2 mg/0.05 mL (40 mg/mL) of FYB203 in a single-dose vial is the same as that of US-Eylea.

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/s/

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